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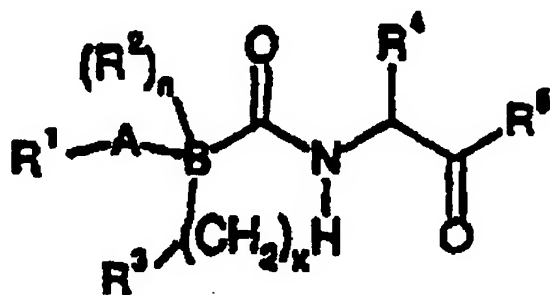
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(54) **NOUVEAUX AMIDES HETEROCYCLIQUEMENT SUBSTITUES
A ACTION DE PROTEASES DE CYSTEINE**

(54) **NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH
CYSTEINE PROTEASE-INHIBITING EFFECT**



(I)

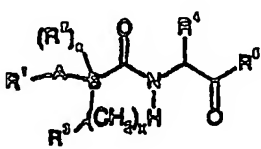
(57) L'invention concerne des amides de la formule générale (I), qui sont des inhibiteurs d'enzymes, notamment de protéases de cystéine.

(57) The invention relates to amides of the general formula (I), which are inhibitors of enzymes, especially cysteine proteases.

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 WELTORGANISATION FÜR GEISTIGES EIGENTUM
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<p>(51) Internationale Patentklassifikation ⁶ : C07D 295/12, A61K 31/50, C07D 403/04, 317/58, 207/06, 215/06, 215/24, 217/04, 213/70, 213/30, C07C 237/32, 311/08, 311/21</p>	A1	<p>(11) Internationale Veröffentlichungsnummer: WO 99/54320</p> <p>(43) Internationales Veröffentlichungsdatum: 28. Oktober 1999 (28.10.99)</p>		
<table style="width: 100%; border: none;"> <tr> <td style="width: 45%; vertical-align: top; padding: 5px;"> <p>(21) Internationales Aktenzeichen: PCT/EP99/02620</p> <p>(22) Internationales Anmeldedatum: 19. April 1999 (19.04.99)</p> <p>(30) Prioritätsdaten: 198 17 460.8 20. April 1998 (20.04.98) DE</p> <p>(71) Anmelder (für alle Bestimmungsstaaten ausser US): BASF AK- TIENGESELLSCHAFT [DE/DE]; D-67056 Ludwigshafen (DE).</p> <p>(72) Erfinder; und (75) Erfinder/Anmelder (nur für US): LUBISCH, Wilfried [DE/DE]; Häuserstrasse 15, D-69115 Heidelberg (DE). MÖLLER, Achim [DE/DE]; Im Zaunrücken 10, D-67269 Grünstadt (DE). TREIBER, Hans-Jörg [DE/DE]; Sperber- weg 1, D-68782 Brühl (DE). KNOPP, Monika [DE/DE]; Karl-Dillinger-Strasse 19, D-67071 Ludwigshafen (DE).</p> <p>(74) Gemeinsamer Vertreter: BASF AKTIENGESELLSCHAFT; D-67056 Ludwigshafen (DE).</p> </td> <td style="width: 55%; vertical-align: top; padding: 5px;"> <p>(81) Bestimmungsstaaten: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, ZA, eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Veröffentlicht <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i></p> <div style="text-align: center; font-size: 1.5em; margin-top: 20px;"> 48969 020602 </div> </td> </tr> </table>			<p>(21) Internationales Aktenzeichen: PCT/EP99/02620</p> <p>(22) Internationales Anmeldedatum: 19. April 1999 (19.04.99)</p> <p>(30) Prioritätsdaten: 198 17 460.8 20. April 1998 (20.04.98) DE</p> <p>(71) Anmelder (für alle Bestimmungsstaaten ausser US): BASF AK- TIENGESELLSCHAFT [DE/DE]; D-67056 Ludwigshafen (DE).</p> <p>(72) Erfinder; und (75) Erfinder/Anmelder (nur für US): LUBISCH, Wilfried [DE/DE]; Häuserstrasse 15, D-69115 Heidelberg (DE). MÖLLER, Achim [DE/DE]; Im Zaunrücken 10, D-67269 Grünstadt (DE). TREIBER, Hans-Jörg [DE/DE]; Sperber- weg 1, D-68782 Brühl (DE). KNOPP, Monika [DE/DE]; Karl-Dillinger-Strasse 19, D-67071 Ludwigshafen (DE).</p> <p>(74) Gemeinsamer Vertreter: BASF AKTIENGESELLSCHAFT; D-67056 Ludwigshafen (DE).</p>	<p>(81) Bestimmungsstaaten: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, ZA, eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Veröffentlicht <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i></p> <div style="text-align: center; font-size: 1.5em; margin-top: 20px;"> 48969 020602 </div>
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<p>(54) Title: NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH CYSTEINE PROTEASE-INHIBITING EFFECT</p> <p>(54) Bezeichnung: NEUE HETEROCYCLISCH SUBSTITUIERTE AMIDE MIT CYSTEIN-PROTEASE HEMMENDER WIRKUNG</p> <div style="text-align: center; margin: 20px 0;">  <div style="margin-left: 10px;">(1)</div> </div> <p>(57) Abstract</p> <p>The invention relates to amides of the general formula (I), which are inhibitors of enzymes, especially cysteine proteases.</p> <p>(57) Zusammenfassung</p> <p>Die Erfindung betrifft Amide der allgemeinen Formel (I), die Inhibitoren von Enzymen, insbesondere Cystein-Proteasen darstellen.</p>				

①A

NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH
CYSTEINE PROTEASE-INHIBITING EFFECT

The present invention relates to novel amides which are inhibitors of enzymes, especially cysteine proteases such as calpain (= calcium dependant cysteine proteases) and its isoenzymes and cathepsins, for example B and L.

10 Calpains are intracellular proteolytic enzymes from the group of cysteine proteases and are found in many cells. Calpains are activated by an increase in the calcium concentration, a distinction being made between calpain I or μ -calpain, which is activated by μ -molar concentrations of calcium ions, and calpain II or m-calpain, which is activated by m-molar concentrations of calcium ions (P. Johnson, Int. J. Biochem. 1990, 22(8), 811-22). Further calpain isoenzymes have now been postulated too (K. Suzuki et al., Biol. Chem. Hoppe-Seyler, 1995, 376(9), 523-9).

20

It is suspected that calpains play an important part in various physiological processes. These include cleavages of regulatory proteins such as protein kinase C, cytoskeletal proteins such as MAP 2 and spectrin, muscle proteins, protein degradation in rheumatoid arthritis, proteins in the activation of platelets, neuropeptide metabolism, proteins in mitosis and others which are listed in M.J. Barrett et al., Life Sci. 1991, 48, 1659-69 and K.K. Wang et al., Trends in Pharmacol. Sci., 1994, 15, 412-9.

30

Elevated calpain levels have been measured in various pathophysiological processes, for example: ischemia of the heart (e.g. myocardial infarct), of the kidney or of the central nervous system (e.g. stroke), inflammations, muscular dystrophies, cataracts of the eyes, injuries to the central nervous system (e.g. trauma), Alzheimer's disease etc. (see K.K. Wang,

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above). It is suspected that there is a connection between these disorders and elevated and persistent intracellular calcium levels. This results in overactivation of calcium-dependent processes, which
5 are then no longer subject to physiological control. Accordingly, overactivation of calpains may also induce pathophysiological processes.

It has therefore been postulated that inhibitors of
10 calpain enzymes may be useful for treating these disorders. Various investigations have confirmed this. Thus, Seung-Chyul Hong et al., Stroke 1994, 25(3), 663-9 and R.T. Bartus et al., Neurological Res. 1995, 17, 249-58 have shown a neuroprotective effect of
15 calpain inhibitors in acute neurodegenerative disorders or ischemias like those occurring after a stroke. Likewise, calpain inhibitors improved the recovery of the memory deficits and neuromotor disturbances occurring after experimental brain trauma (K.E. Saatman
20 et al. Proc. Natl. Acad. Sci. USA, 1996, 93, 3428-3433). C.L. Edelstein et al., Proc. Natl. Acad. Sci. USA, 1995, 92, 7662-6, found a protective effect of calpain inhibitors on kidneys damaged by hypoxia. Yoshida, Ken Ischi et al., Jap. Circ. J. 1995, 59(1),
25 40-8, were able to show beneficial effects of calpain inhibitors after cardiac damage produced by ischemia or reperfusion. Since the release of the β -AP4 protein is inhibited by calpain inhibitors, a potential therapeutic use for Alzheimer's disease has been
30 proposed (J. Higaki et al., Neuron, 1995, 14, 651-59). The release of interleukin-1 α is likewise inhibited by calpain inhibitors (N. Watanabe et al., Cytokine 1994, 6(6), 597-601). It has further been found that calpain inhibitors have cytotoxic effects on tumor cells
35 (E. Shiba et al. 20th Meeting Int. Ass. Breast Cancer Res., Sendai Jp, 1994, 25-28 Sept., Int. J. Oncol. 5 (Suppl.), 1994, 381).

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Further possible uses of calpain inhibitors are detailed in K.K. Wang, Trends in Pharmacol. Sci., 1994, 15, 412-8.

- 5 Calpain inhibitors have already been described in the literature. However, these are predominantly either irreversible or peptide inhibitors. Irreversible inhibitors are usually alkylating substances and have the disadvantage that they react nonselectively or are
- 10 unstable in the body. Thus, these inhibitors often show unwanted side effects such as toxicity, and are accordingly of limited use or unusable. The irreversible inhibitors can be said to include, for example, the epoxides E 64 (E.B. McGowan et al.,
- 15 Biochem. Biophys. Res. Commun. 1989, 158, 432-5), α -halo ketones (H. Angliker et al., J. Med. Chem. 1992, 35, 216-20) or disulfides (R. Matsueda et al., Chem. Lett. 1990, 191-194).
- 20 Many known reversible inhibitors of cysteine proteases such as calpain are peptide aldehydes, in particular dipeptide and tripeptide [sic] aldehydes such as, for example, Z-Val-Phe-H (MDL 28170) (S. Mehdi, Trends [sic] in Biol. Sci. 1991, 16, 150-3). Under physiological
- 25 conditions, peptide aldehydes have the disadvantage that, owing to the high reactivity, they are often unstable, may be rapidly metabolized and are prone to nonspecific reactions which may cause toxic effects (J.A. Fehrentz and B. Castro, Synthesis 1983, 676-78.
- 30 JP 08183771 (CA 1996, 605307) and EP 520336 have described aldehydes derived from 4-piperidinoylamides [sic] and 1-carboxypiperidino-4-ylamides [sic] as calpain inhibitors. However, the aldehydes which are claimed herein and are derived from amides of the
- 35 general structure I with heteroaromatic substituents have not previously been described.

Peptide ketone derivatives are likewise inhibitors of cysteine proteases, in particular calpains. Thus, for

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example, ketone derivatives where the keto group is activated by an electron-attracting group such as CF_3 are known to be inhibitors of serine proteases. In the case of cysteine proteases, derivatives with ketones activated by CF_3 or similar groups have little or no activity (M.R. Angelastro et al., J. Med. Chem. 1990, 33, 11-13). Surprisingly, to date only ketone derivatives in which, on the one hand, leaving groups in the α position cause irreversible inhibition and, on the other hand, the keto group is activated by a carboxylic acid derivative have been found to be effective inhibitors of calpain (see M.R. Angelastro et al., see above; WO 92/11850; WO 92,12140; WO 94/00095 and WO 95/00535). However, only peptide derivatives of these keto amides and keto esters have been described as effective (Zhaozhao Li et al., J. Med. Chem. 1993, 36, 3472-80; S.L. Harbenson et al., J. Med. Chem. 1994, 37, 2918-29 and see above M.R. Angelastro et al.).

Ketobenzamides have already been described in the literature. Thus, the keto ester $\text{PhCO-Abu-COOCH}_2\text{CH}_3$ has been described in WO 91/09801, WO 94/00095 and 92/11850. The analogous phenyl derivative $\text{Ph-CONH-CH(CH}_2\text{Ph)-CO-COCOOCH}_3$ was, however, found to be only a weak calpain inhibitor in M.R. Angelastro et al., J. Med. Chem. 1990, 33, 11-13. This derivative is also described in J.P. Burkhardt, Tetrahedron Lett., 1988, 3433-36. The significance of the substituted benzamides has, however, never been investigated to date.

In a number of therapies, such as [lacuna] stroke, the active ingredients are administered intravenously, for example as infusion solution. To do this it is necessary to have available substances, in this case calpain inhibitors, which have adequate solubility in water so that an infusion solution can be prepared. Many of the described calpain inhibitors have, however, the disadvantage that they have only low or no

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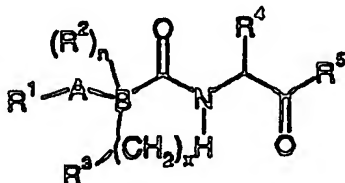
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solubility in water and thus are unsuitable for intravenous administration. Active ingredients of this type can be administered only with ancillary substances intended to confer solubility in water (cf. R.T. Bartus
 5 et al. J. Cereb. Blood Flow Metab. 1994, 14, 537-544). These ancillary substances, for example polyethylene glycol, often have side effects, however, or are even incompatible. A non-peptide calpain inhibitor which is soluble in water without ancillary substances would
 10 thus be a great advantage. No such inhibitor has been described to date, and it would thus be novel.

Substituted non-peptide aldehydes, keto carboxylic esters and keto amide derivatives were described in the
 15 present invention. These compounds are novel and surprisingly show the possibility of obtaining potent non-peptide inhibitors of cysteine proteases, such as, for example, calpain, by incorporating rigid structural fragments. In addition, all the present compounds of
 20 the general formula I have at least one aliphatic amine radical and are thus able to bind [sic] salts with acids. A large number of these substances are soluble in water in a 0.5% strength solution at pH 0.4-5 and thus the show the required profile for intravenous
 25 administration as is necessary, for example, for stroke therapy.

The present invention relates to amides of the general formula I

30



and their tautomeric and isomeric forms, possible enantiomeric and diastereomeric forms, and possible
 35 physiologically tolerated salts, in which the variables

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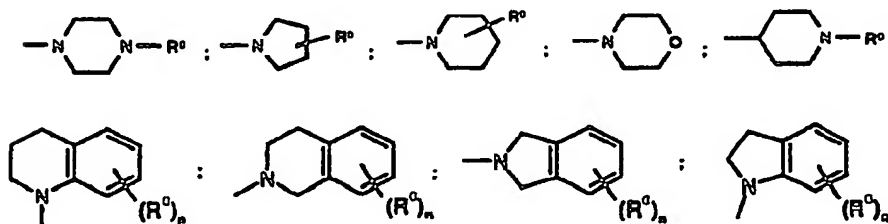
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have the following meanings:

5 R^1 can be hydrogen, C_1 - C_6 -alkyl, branched and unbranched, phenyl, naphthyl, quinolyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinazolyl, quinoxalyl, thienyl, benzothienyl, benzofuranyl, furanyl and indolyl, it being possible for the rings also to be substituted by up to 3 R^6 radicals, and

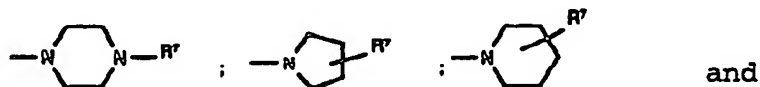
10 R^2 are hydrogen, C_1 - C_6 -alkyl, branched or unbranched, O - C_1 - C_6 -alkyl, branched or unbranched, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_1 - C_6 -alkyl-phenyl, C_2 - C_6 -alkenyl-phenyl, C_2 - C_6 -alkynyl-phenyl, OH, Cl, F, Br, I, CF_3 , NO_2 , NH_2 , CN, COOH, COO- C_1 - C_4 -alkyl, NHCO- C_1 - C_4 -alkyl, NHCO-phenyl, CONHR⁹, NHSO₂- C_1 - C_4 -alkyl, NHSO₂-phenyl, SO₂- C_1 - C_4 -alkyl and SO₂-phenyl, and

20 R^3 can be NR^7R^8 or a ring such as



25 R^4 is $-C_1$ - C_6 -alkyl, branched or unbranched, which may also carry a phenyl, pyridyl or naphthyl ring which is in turn substituted by a maximum of two R^6 radicals, and

30 R^5 is hydrogen, COOR¹¹ and CO-Z in which Z is $NR^{12}R^{13}$ and



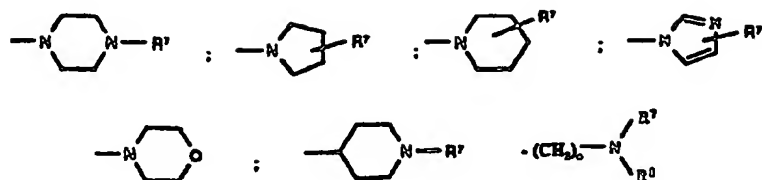
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- 5 R^6 is hydrogen, C_1 - C_4 -alkyl, branched or unbranched,
-O- C_1 - C_4 -alkyl, OH, Cl, F, Br, I, CF_3 , NO_2 , NH_2 , CN,
COOH, COO- C_1 - C_4 -alkyl, -NHCO- C_1 - C_4 -alkyl,
-NHCO-phenyl, -NHSO₂- C_1 - C_4 -alkyl, -NHSO₂-phenyl,
-SO₂- C_1 - C_4 -alkyl and -SO₂-phenyl, and
- 10 R^7 is hydrogen, C_1 - C_6 -alkyl, linear or branched, and
which may be substituted by a phenyl ring which
itself may also be substituted by one or two R^{10}
radicals, and
- 15 R^8 is hydrogen, C_1 - C_6 -alkyl, linear or branched, which
may be substituted by a phenyl ring which may
itself also be substituted by one or two R^{10}
radicals, and
- 20 R^9 is hydrogen, C_1 - C_6 -alkyl, branched or unbranched,
which may also carry a substituent R^{16} , or phenyl,
pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl,
naphthyl, quinolyl, imidazolyl, which may also
carry one or two substituents R^{14} , and
- 25 R^{10} can be hydrogen, C_1 - C_4 -alkyl, branched or
unbranched, -O- C_1 - C_4 -alkyl, OH, Cl, F, Br, I, CF_3 ,
 NO_2 , NH_2 , CN, COOH, COO- C_1 - C_4 -alkyl,
-NHCO- C_1 - C_4 -alkyl, -NHCO-phenyl, -NHSO₂- C_1 - C_4 -alkyl,
-NHSO₂-phenyl, -SO₂- C_1 - C_4 -alkyl and -SO₂-phenyl
- 30 R^{11} is hydrogen, C_1 - C_6 -alkyl, linear or branched, and
which may be substituted by a phenyl ring which
may itself also be substituted by one or two R^{10}
radicals, and
- 35 R^{12} is hydrogen, C_1 - C_6 -alkyl, branched and unbranched,
and

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[sic]

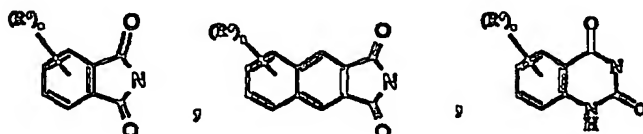
5 R^{13} is hydrogen, C_1 - C_6 -alkyl, branched or unbranched, which may also be substituted by a phenyl ring which may also carry an R^{10} radical, and by [lacuna] and

10 R^{14} is hydrogen, C_1 - C_6 -alkyl, branched or unbranched, O - C_1 - C_6 -alkyl, branched or unbranched, OH, Cl, F, Br, I, CF_3 , NO_2 , NH_2 , CN, COOH, COO - C_1 - C_4 -alkyl, or two R^{14} radicals may represent a bridge $OC(R^{15})_2O$, and

15 R^{15} is hydrogen, C_1 - C_6 -alkyl, branched and unbranched, and

20 R^{16} can be a phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, pyrrolyl, naphthyl, quinolyl, imidazolyl ring, which may also carry one or two substituents R^6 , and

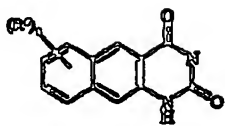
25 A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-(CH_2)_o-SO-(CH_2)_m-$, $-(CH_2)_o-SO_2-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$, $-CO-CH=CH-$, $-(CH_2)_o-CO-(CH_2)_m-$, $-(CH_2)_m-NHCO-(CH_2)_o-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-NHSO_2-(CH_2)_o-$, $-NH-CO-CH=CH-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, $-CH=CH-CONH-$ and



and

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[sic]

R¹-A together are also

[lacuna]

and

5

B is phenyl, pyridine, pyrimidine, pyrazine, imidazole and thiazole and

x is 1, 2 or 3, and

10

n is a number 0, 1 or 2, and

m, o is, independently of one another, a number 0, 1, 2, 3 or 4.

15

The compounds of the formula I can be employed as racemates, as enantiomerically pure compounds or as diastereomers. If enantiomerically pure compounds are required, these can be obtained, for example, by carrying out a classical racemate resolution with the compounds of the formula I or their intermediates using a suitable optically active base or acid. On the other hand, the enantiomeric compounds can likewise be prepared by using commercially purchasable compounds, for example optically active amino acids such as phenylalanine, tryptophan and tyrosine.

The invention also relates to compounds which are mesomers or tautomers of compounds of the formula I, for example those in which the aldehyde or keto group in formula I is in the form of an enol tautomer.

The invention further relates to the physiologically tolerated salts of the compounds I which can be obtained by reacting compounds I with a suitable acid

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or base. Suitable acids and bases are listed, for example, in Fortschritte der Arzneimittelforschung, 1966, Birkhäuser Verlag, Vol. 10, pp. 224-285. These include, for example, hydrochloric acid, citric acid, 5 tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid etc., and sodium hydroxide, lithium hydroxide, potassium hydroxide and tris.

The amides I according to the invention can be prepared 10 in various ways which has [sic] been outlined in the synthesis scheme.

Synthesis scheme

Heterocyclic carboxylic acids II are linked to suitable 15 amino alcohols III to give the corresponding amides IV. Conventional peptide coupling methods are used for this, as detailed either in C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, page 972 et seq., or in Houben-Weyl, Methoden der 20 organischen Chemie, 4th edition, E5, Chapter V. It is preferred to use "activated" acid derivatives of II, with the acid group COOH being converted into a group COL. L is a leaving group such as, for example, Cl, imidazole and N-hydroxybenzotriazole. This activated 25 acid is then reacted with amines to give the amides IV. The reaction takes place in anhydrous inert solvents such as methylene chloride, tetrahydrofuran and dimethylformamide at temperatures from -20 to +25°C.

30 These alcohol derivatives IV can be oxidized to the aldehyde derivatives I according to the invention. Various conventional oxidation reactions can be used for this (see C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, page 604 et seq.) 35 such as, for example, Swern and Swern-analogous oxidations (T.T. Tidwell, Synthesis, 1990, 857-70), sodium hypochloride [sic]/TEMPO (S.L. Harbenson et al., see above) or Dess-Martin (J. Org. Chem. 1983, 48, 4155). Preferably used for this are inert aprotic

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solvents such as dimethylformamide, tetrahydrofuran or methylene chloride with oxidizing agents such as DMSO/py x SO₃ or DMSO/oxalyl chloride at temperatures from -50 to +25°C, depending on the method (see above
5 literature).

Alternatively, the carboxylic acid II can be reacted with amino hydroxamic acid derivatives VI to give benzamides VII. The reaction in this case is carried
10 out in the same way as for preparing IV. The hydroxamic derivatives VI can be obtained from the protected amino acids V by reaction with a hydroxylamine. An amide preparation process already described is also used in this case. Elimination of the protective group X, for
15 example Boc, takes place in a normal way, for example with trifluoroacetic acid. The amide hydroxamic acids VII obtained in this way can be converted by reduction into the aldehydes I according to the invention. The reducing agent used for this is, for example, lithium
20 aluminum hydride at temperatures from -60 to 0°C in inert solvents such as tetrahydrofuran or ether.

Carboxylic acids or acid derivatives such as esters IX (P = COOR', COSR') can also be prepared in analogy to
25 the last process and can likewise be converted by reduction into the aldehydes I according to the invention. These processes are listed in R.C. Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, pages 619-26.

30

The amides I according to the invention, which have heterocyclic substituents and have a keto amide or keto ester group, can be prepared in various ways which have been outlined in synthesis schemes 2 and 3.

35

The carboxylic esters IIa are converted, where appropriate, with acids or bases such as lithium hydroxide, sodium hydroxide or potassium hydroxide in aqueous medium or in mixtures of water and organic

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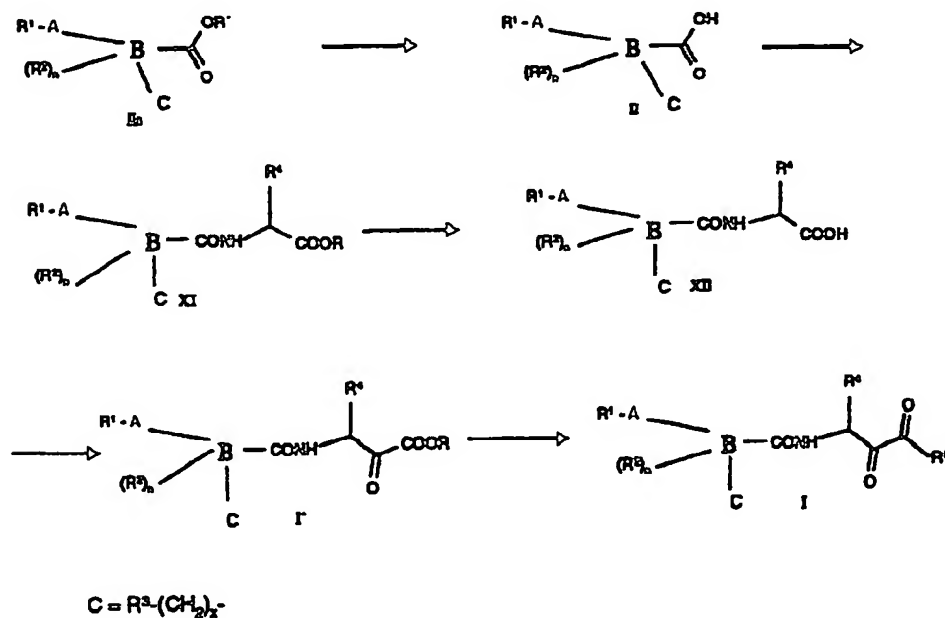
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solvents such as alcohols or tetrahydrofuran at room temperature or elevated temperatures, such as 25-100°C, into the acids II.

- 5 These acids II are linked to an α -amino acid derivative using customary conditions which are listed, for example, in Houben-Weyl, Methoden der organischen Chemie, 4th edition, E5, Chapter V, and C.R. [sic] Larock, Comprehensive Organic Transformations, VCH
- 10 Publisher, 1989, Ch. 9.

- For example, the carboxylic acids II are converted into the "activated" acid derivatives IIb = Y-COL, where L is a leaving group such as Cl, imidazole and
- 15 N-hydroxybenzotriazole, and then converted into the derivative XI by adding an amino acid derivative $\text{H}_2\text{N}-\text{CH}(\text{R}^3)-\text{COOR}$. This reaction takes place in anhydrous inert solvents such as methylene chloride, tetrahydrofuran and dimethylformamide at temperatures
- 20 from -20 to +25°C.

Scheme 1



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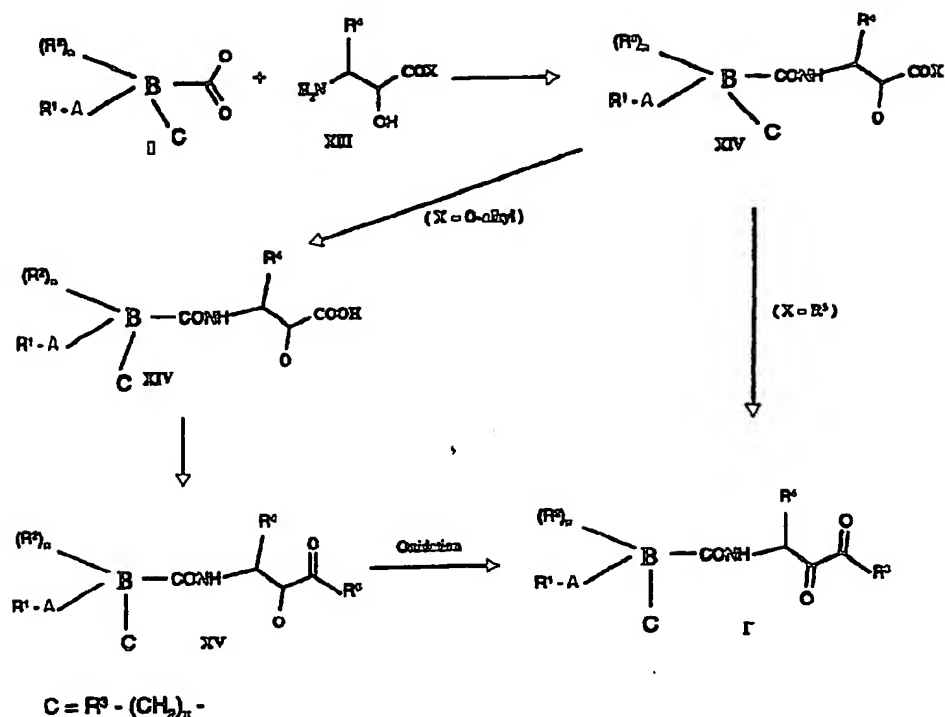
The derivatives XI, which are usually esters, are converted into the keto carboxylic acids XII by hydrolysis analogous to that described above. The keto esters I' are prepared in a Dakin-West-analogous reaction using a method of ZhaoZhao Li et al., J. Med. Chem., 1993, 36, 3472-80. This entails a [sic] carboxylic acids such as XII being reacted with oxalic monoester chloride at elevated temperature (50-100°C) in solvents such as, for example, tetrahydrofuran, and the product obtained in this way then being reacted with bases such as sodium ethanolate in ethanol at temperatures of 25-80°C to give the keto ester I' according to the invention. The keto esters I' can be hydrolyzed as described above for example to keto carboxylic acids according to the invention.

The reaction to give keto benzamides I' likewise takes place in analogy to the method of ZhaoZhao Li et al. (see above). The keto group in I' is protected by adding 1,2-ethanedithiol with Lewis acid catalysis, such as, for example, boron trifluoride etherate, in inert solvents such as methylene chloride at room temperature, resulting in a dithiane. These derivatives are reacted with amines R^3-H in polar solvents such as alcohols at temperatures of 0-80°C, resulting in the keto amides I ($R^4 = Z$ or NR^7R^8).

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Scheme 2



- 5 An alternative method is depicted in scheme 2. The keto carboxylic acids II are reacted with amino hydroxy carboxylic acid derivatives XIII (for preparation of XIII, see S.L. Harbenson et al., J. Med. Chem. 1994, 37, 2918-29 or J.P. Burkhardt et al. Tetrahedron Lett. 1988, 29, 3433-3436) using customary peptide coupling methods (see above, Houben-Weyl), resulting in amides XIV. These alcohol derivatives XIV can be oxidized to the keto carboxylic acid derivatives I according to the invention. It is possible to use for this various
- 15 customary oxidation reactions (see C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, [lacuna] page 604 et seq.) such as, for example, Swern and Swern-analogous oxidations, preferably dimethyl sulfoxide/pyridine-sulfur trioxide complex in solvents
- 20 such as methylene chloride or tetrahydrofuran, where appropriate with the addition of dimethyl sulfoxide, at room temperature or temperatures from -50 to 25°C (T.T. Tidwell, Synthesis 1990, 857-70) or sodium

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hypochloride [sic]/TEMPO (S.L. Harbenson et al., see above).

In the case of α -hydroxy esters XIV ($X = O\text{-alkyl}$),
5 these can be hydrolyzed to carboxylic acids XV using
methods analogous to those above, but preferably using
lithium hydroxide in water/tetrahydrofuran mixtures at
room temperature. Other esters or amides XVI are
10 prepared by reaction with alcohols or amines under
coupling conditions described above. The alcohol
derivative XVI can be oxidized to give keto carboxylic
acid derivatives I according to the invention.

The preparation of the carboxylic esters II had already
15 been described for some instances, or it takes place by
usual chemical methods.

Compounds in which X is a bond are prepared by
conventional aromatic coupling, for example Suzuki
20 coupling with boric acid derivatives and halides with
palladium catalysis or copper-catalyzed coupling of
aromatic halides. The alkyl-bridged radicals
($X = -(\text{CH}_2)_n-$) can be prepared by reducing the analogous
ketones or by alkylating the organolithium, e.g. ortho-
25 phenyloxazolidines, or other organometallic compounds
(cf. I.M. Dordor et al., J. Chem. Soc. Perkins Trans.
I, 1984, 1247-52).

Ether-bridged derivatives are prepared by alkylating
30 the corresponding alcohols or phenols with halides.

The sulfoxides and sulfones can be obtained by
oxidizing the corresponding thioethers.

35 Alkene- and alkyne-bridged compounds are prepared, for
example, by the Heck reaction from aromatic halides and
corresponding alkenes and alkynes (cf. I. Sakamoto et
al., Chem. Pharm. Bull., 1986, 34, 2754-59).

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The chalcones are produced by condensing acetophenones with aldehydes and can, where appropriate, be converted into the analogous alkyl derivatives by hydrogenation.

- 5 Amides and sulfonamides are prepared from the amines and acid derivatives in analogy to the methods described above.

- 10 The dialkylaminoalkyl substituents are obtained by reductive amination of the aldehyde derivatives with the appropriate amines in the presence of boron hydrides such as the BH_3 /pyridine complex or or [sic] NaBH_3CN (A.F. Abdel-Magid, C.A. Maryanoff, K.G. Carson, Tetrahedron Lett. 10990 [sic], 31, 5595; A.E. Moormann, 15 Synth. Commun. 1993, 23, 789).

- The amides I with heterocyclic substituents of the present invention are inhibitors of cysteine proteases, especially cysteine proteases such as calpains I and II 20 and cathepsins B and L.

- The inhibitory effect of the amides I with heterocyclic substituents has been determined using enzyme assays known from the literature, determining as criterion of 25 effect a concentration of the inhibitor at which 50% of the enzyme activity is inhibited ($= \text{IC}_{50}$). The amides I were measured in this way for their inhibitory effect on calpain I, calpain II and cathepsin B.

30 Cathepsin B assay

The inhibition of cathepsin B was determined by a method analogous to that of S. Hasnain et al., J. Biol. Chem., 1993, 268, 235-40.

35

2 μl of an inhibitor solution prepared from inhibitor and DMSO (final concentrations: 100 μM to 0.01 μM) are added to 88 μl of cathepsin B (cathepsin B from human liver (Calbiochem), diluted to 5 units in 500 μM

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buffer). This mixture is preincubated at room temperature (25°C) for 60 minutes and then the reaction is started by adding 10 µl of 10 mM Z-Arg-Arg-pNA (in buffer with 10% DMSO). The reaction is followed in a microtiter plate reader at 405 nM [sic] for 30 minutes. The IC₅₀s are then determined from the maximum gradients.

Calpain I and II assay

10

The testing of the inhibitory properties of calpain inhibitors takes place in buffer with 50 mM tris-HCl, pH 7.5; 0.1 M NaCl; 1 mM dithiotreitol [sic]; 0.11 mM CaCl₂, using the fluorogenic calpain substrate Suc-Leu-Tyr-AMC (25 mM dissolved in DMSO, Bachem/Switzerland). Human µ-calpain is isolated from erythrocytes, and enzyme with a purity > 95%, assessed by SDS-PAGE, Western blot analysis and N-terminal sequencing, is obtained after several chromatographic steps (DEAE-Sepharose, phenyl-Sepharose, Superdex 200 and blue Sepharose). The fluorescence of the cleavage product 7-amino-4-methylcoumarin (AMC) is followed in a Spex Fluorolog fluorimeter at λ_{ex} = 380 nm and λ_{em} = 460 nm. The cleavage of the substrate is linear in a measurement range of 60 min., and the autocatalytic activity of calpain is low, if the tests are carried out at temperatures of 12°C. The inhibitors and the calpain substrate are added to the test mixture as DMSO solutions, and the final concentration of DMSO ought not to exceed 2%.

In a test mixture, 10 µl of substrate (250 µM final) and then 10 µl of µ-calpain (2 µg/ml final, i.e. 18 nM) are added to a 1 ml cuvette containing buffer. The calpain-mediated cleavage of the substrate is measured for 15 - 20 min. Then 10 µl of inhibitor (50-100 µM solution in DMSO) are added and the inhibition of cleavage is measured for a further 40 min.

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K_i values are determined using the classical equation for reversible inhibition:

(Methods in Enzymology,)

- 5 $K_i = I(v_0/v_i)-1$; where I = inhibitor concentration,
v0 = initial rate before addition of the inhibitor;
vi = reaction rate at equilibrium.

The rate is calculated from $v = \text{AMC liberation/time}$,
10 i.e. height/time.

Calpain is an intracellular cysteine protease. Calpain inhibitors must pass through the cell membrane in order to prevent intracellular proteins from being broken
15 down by calpain. Some known calpain inhibitors, such as, for example, E 64 and leupeptin, cross cell membranes only poorly and accordingly show only a poor effect on cells, although they are good calpain inhibitors. The aim is to find compounds better able to
20 cross membranes. Human platelets are used to demonstrate the ability of calpain inhibitors to cross membranes.

Calpain-mediated breakdown of tyrosine kinase pp60src
25 in platelets

Tyrosine kinase pp60src is cleaved by calpain after activation of platelets. This has been investigated in detail by Oda et al. in J. Biol. Chem., 1993, Vol. 268,
30 12603-12608. This revealed that the cleavage of pp60src can be prevented by calpeptin, a calpain inhibitor. The cellular efficacy of our substances was tested based on this publication. Fresh, citrated, human blood was centrifuged at 200 g for 15 min. The platelet-rich
35 plasma was pooled and diluted 1:1 with platelet buffer (platelet buffer: 68 mM NaCl, 2.7 mM KCl, 0.5 mM $\text{MgCl}_2 \times 6 \text{ H}_2\text{O}$, 0.24 mM $\text{NaH}_2\text{PO}_4 \times \text{H}_2\text{O}$, 12 mM NaHCO_3 , 5.6 mM glucose, 1 mM EDTA, pH 7.4). After a centrifugation step and washing step with platelet

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buffer, the platelets were adjusted to 10^7 cells/ml. The human platelets were isolated at RT.

In the assay mixture, isolated platelets (2×10^6) were preincubated with various concentrations of inhibitors (dissolved in DMSO) at 37°C for 5 min. The platelets were then activated with $1 \mu\text{M}$ ionophore A23187 and 5 mM CaCl_2 . After incubation for 5 min., the platelets were briefly centrifuged at 13,000 rpm, and the pellet was taken up SDS sample buffer (SDS sample buffer: 20 mM Tris-HCl, 5 mM EDTA, 5 mM EGTA, 1 mM DTT, 0.5 mM PMSF, 5 $\mu\text{g/ml}$ leupeptin, 10 $\mu\text{g/ml}$ pepstatin, 10% glycerol and 1% SDS). The proteins were fractionated in a 12% gel, and pp60src and its 52 kDa and 47 kDa cleavage products were identified by Western blotting. The polyclonal rabbit antibody used, anti-cys-src (pp60^{c-src}), was purchased from Biomol Feinchemikalien (Hamburg). This primary antibody was detected using a second, HRP-coupled goat antibody (Boehringer Mannheim, FRG). The Western blotting was carried out by known methods.

The cleavage of pp60src was quantified by densitometry, using as controls unactivated (control 1: no cleavage) and ionophore- and calcium-treated platelets (control 2: corresponds to 100% cleavage). The ED_{50} corresponds to the concentration of inhibitor at which the intensity of the color reaction is reduced by 50%.

Glutamate-induced cell death in cortical neurones

30

The test was carried out as in Choi D.W., Maulucci-Gedde M.A. and Kriegstein A.R., "Glutamate neurotoxicity in cortical cell culture". J. Neurosci. 1989, 7, 357-368.

35

The cortex halves were dissected out of 15-day old mouse embryos and the single cells were obtained enzymatically (trypsin). These cells (glia and cortical neurones) are seeded out in 24-well plates. After three

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days (laminin-coated plates) or seven days (ornithine-coated plates), the mitosis treatment is carried out with FDU (5-fluoro-2-deoxyuridines [sic]). 15 days after preparation of the cells, cell death is induced
5 by adding glutamate (15 minutes). After removal of glutamate, the calpain inhibitors are added. 24 hours later, the cell damage is estimated by determining lactate dehydrogenase (LDH) in the cell culture supernatant.

10

It is postulated that calpain is also involved in apoptotic cell death (M.K.T. Squier et al., J. Cell. Physiol. 1994, 159, 229-237; T. Patel et al. Faseb Journal 1996, 590, 587-597). For this reason, in
15 another model, cell death was induced in a human cell line with calcium in the presence of a calcium ionophore. Calpain inhibitors must get inside the cell and inhibit calpain there in order to prevent the induced cell death.

20

Calcium-mediated cell death in NT2 cells

Cell death can be induced in the human cell line NT2 by calcium in the presence of the ionophore A 23187.
25 10^5 cells/well were plated out in microtiter plates 20 hours before the test. After this period, the cells were incubated with various concentrations of inhibitors in the presence of 2.5 μ M ionophore and 5 mM calcium. 0.05 ml of XTT (Cell Proliferation Kit II,
30 Boehringer Mannheim) was added to the reaction mixture after 5 hours. The optical density was determined approximately 17 hours later, in accordance with the manufacturer's information, in an SLT Easy Reader EAR 400. The optical density at which half the cells
35 have died is calculated from the two controls with cells without inhibitors incubated in the absence and presence of ionophore.

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Elevated glutamate activities occur in a number of neurological disorders of psychological disturbances and lead to states of overexcitation or toxic effects in the central nervous system (CNS). The effects of glutamate are mediated by various receptors. Two of these receptors are classified, in accordance with the specific agonists, as NMDA receptor and AMPA receptor. Antagonists to these glutamate-mediated effects can thus be employed for treating these disorders, in particular for therapeutic use for neurodegenerative disorders such as Huntington's chorea and Parkinson's disease, neurotoxic impairments after hypoxia, anoxia, ischemia and after lesions like those occurring after stroke and trauma, or else as antiepileptics (cf. Arzneim. Forschung 1990, 40, 511-514; TIPS, 1990, 11, 334-338; Drugs of the Future 1989, 14, 1059-1071). De [sic]

Protection from cerebral overexcitation by excitatory amino acids (NMDA and AMPA antagonism in mice)

Intracerebral administration of excitatory amino acids (EAA) induces such drastic overexcitation that it leads to convulsions and death of the animals (mice) within a short time. These signs can be inhibited by systemic, e.g. intraperitoneal, administration of centrally acting substances (EAA antagonists). Since excessive activation of EAA receptors in the central nervous system plays a significant part in the pathogenesis of various neurological disorders, it is possible to infer from the detected EAA antagonism in vivo that the substances may have therapeutic uses for such CNS disorders. As a measure of the efficacy of the substances, an ED₅₀ was determined, at which 50% of the animals are free of signs, owing to the previous i.p. administration of the measured substance, by a fixed dose of either NMDA or AMPA.

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The amides I with heterocyclic substituents are inhibitors of cysteine derivatives [sic] such as calpain I and II and cathepsin B and L, and can thus be used to control diseases associated with an elevated activity of calpain enzymes or cathepsin enzymes. The present amides I can accordingly be used to treat neurodegenerative disorders occurring after ischemia, trauma, subarachnoid hemorrhages and stroke, and neurodegenerative disorders such as multi-infarct dementia, Alzheimer's disease, Huntington's disease and epilepsies and, in addition, to treat damage to the heart after cardiac ischemia, damage to the kidneys after renal ischemia, skeletal muscle damage, muscular dystrophies, damage caused by proliferation of smooth muscle cells, coronary vasospasms, cerebral vasospasms, cataracts of the eyes, restenosis of the blood vessels after angioplasty. In addition, the amides I may be useful in the chemotherapy of tumors and metastasis thereof and for treating disorders in which an elevated interleukin-1 level occurs, such as inflammation and rheumatic disorders.

The pharmaceutical preparations according to the invention comprise a therapeutically effective amount of the compounds I in addition to conventional pharmaceutical ancillary substances.

The active ingredients can be present in the usual concentrations for local external use, for example in dusting powders, ointments or sprays. As a rule, the active ingredients are present in an amount of from 0.001 to 1% by weight, preferably 0.001 to 0.1% by weight.

For internal use, the preparations are administered in single doses. From 0.1 to 100 mg are given per kg of body weight in a single dose. The preparation may be administered in one or more doses each day, depending on the nature and severity of the disorders.

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The pharmaceutical preparations according to the invention comprise, apart from the active ingredient, the customary excipients and diluents appropriate for the required mode of administration. For local external use it is possible to use pharmaceutical ancillary substances such as ethanol, isopropanol, ethoxylated castor oil, ethoxylated hydrogenated castor oil, polyacrylic acid, polyethylene glycol, polyethylene glyco [sic] stearate, ethoxylated fatty alcohols, liquid paraffin, petrolatum and wool fat. Suitable examples for internal use are lactose, propylene glycol, ethanol, starch, talc and polyvinylpyrrolidone.

It is also possible for antioxidants such as tocopherol and butylated hydroxyanisole, and butylated hydroxytoluene, flavor-improving additives, stabilizers, emulsifiers and lubricants to be present.

The substances which are present in the preparation in addition to the active ingredient, and the substances used in producing the pharmaceutical preparations, are toxicologically acceptable and compatible with the active ingredient in each case. The pharmaceutical preparations are produced in a conventional way, for example by mixing the active ingredient with other [sic] customary excipients and diluents.

The pharmaceutical preparations can be administered in various ways, for example orally, parenterally, such as intravenously by infusion, subcutaneously, intraperitoneally and topically. Thus, possible presentations are tablets, emulsions, solutions for infusion and injection, pastes, ointments, gels, creams, lotions, dusting powders and sprays.

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ExamplesExample 1

5 2-(((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-yl)amide

a) Methyl 2-(4-phenyl-1-piperazinylmethyl)benzoate

10 10.0 g of methyl 2-chloromethylbenzoate, 15 g of
potassium carbonate, 8.8 g of N-phenylpiperazine
and a spatula-tip of 18-crown-6 in 200 ml of DMF
were heated at 100°C for 5 h and then stirred at
room temperature for 60 h. The excess potassium
15 carbonate was filtered off, the filtrate was
concentrated, and the residue was partitioned
between water and ethyl acetate. Drying of the
organic phase over magnesium sulfate and removal
of the solvent resulted in 16.8 g (100%) of the
20 product.

b) 2-(4-phenyl-1-piperazinylmethyl)benzoic acid

25 16.8 g of intermediate 1a were introduced into
150 ml of THF, and 1.7 g of LiOH in 150 ml of
water were added at room temperature. The cloudy
solution was clarified by adding 10 ml of MeOH.
The reaction mixture was stirred at room
temperature for 12 h and hydrolyzed with an
30 equimolar amount of 1 M HCl. The reaction mixture
was evaporated to dryness, and the residue was
taken up in methanol/toluene. Removal of the
solvent resulted in 15.2 g (86%) of the product,
which still contained salt.

35

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- c) 2-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-ol-2-yl)amide

5 3.0 g of intermediate 1b and 3 ml of triethylamine were introduced into 50 ml of DMF. 5 g of sodium sulfate were added and the mixture was stirred for 30 min. 1.5 g of phenylalaninol, 1.4 g of HOBT and 2.1 g of EDC were successively added at 0°C, and the mixture was stirred at room temperature
10 overnight. The reaction mixture was poured into distilled water, made alkaline with NaHCO₃, saturated with NaCl and extracted three times with 100 ml of methylene chloride. The organic phases were washed twice with water and dried over
15 magnesium sulfate. Removal of the solvent resulted in 2.5 g (59%) of the product.

- d) 2-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-ol-2-yl)amide

20 2.3 g of intermediate 1c were introduced into 50 ml of DMSO in the presence of 2.4 g of triethylamine, and 2.5 g of SO₃/pyridine complex were added. The mixture was stirred at room
25 temperature overnight. The mixture was poured into 250 ml of distilled water, made alkaline with NaHCO₃, saturated with NaCl and extracted with 100 ml of methylene chloride, and the organic phase was dried over magnesium sulfate. After
30 removal of the solvent, the residue was dissolved in THF, and the hydrochloride was precipitated with HCl in dioxane. The precipitate was filtered off with suction and washed several times with ether, resulting in 1.9 g (71%) of the product.

35

¹H-NMR (d₆-DMSO): δ = 2.9 (2H), 3.0-3.3 (8H), 4.1-4.5 (2H), 4.7 (1H), 6.8-7.7 (14H), 9.3 (1H), 9.8 (1H) ppm.

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Example 2

2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-yl)amide

5

- a) Methyl 2-((4-benzyl-1-piperazinyl)methyl)benzoate [sic]

10.0 g of methyl 2-chlorobenzoate and 9.6 g of N-benzylpiperazine were reacted in 200 ml of DMF in the presence of 15 g of potassium carbonate at 100°C in analogy to Example 1a, resulting in 17.6 g (100%) of the product.

- 15 b) 2-((4-Benzyl-1-piperazinyl)methyl)benzoic acid [sic]

17.5 g of intermediate 2a in 150 ml of THF were hydrolyzed with 1.6 g of LiOH in 150 ml of water in analogy to Example 1b, resulting in 9.1 g (54%) of the product.

- c) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-yl)amide

25

3.0 g of intermediate 2b were reacted in 60 ml of DMF with 3 ml of triethylamine, 1.5 g of phenylalaninol, 1.3 g of HOBT and 2.0 g of EDC in analogy to Example 1c, resulting in 2.0 g (46%) of the product.

30

- d) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-yl)amide

1.5 g of intermediate 2c were oxidized in 40 ml of DMSO with 1.9 g of SO₃/pyridine complex in 20 ml of DMSO in the presence of 2.3 ml of triethylamine in analogy to Example 1d, resulting in 0.4 g (21%) of the product in the form of the fumarate.

35

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¹H-NMR (d₆-DMSO): δ = 2.1-2.3 (8H), 2.9-3.0 (1H), 3.3-3.6 (6H), 4.5 (1H), 6.6 (2H), 7.1-7.7 (14H), 9.7 (1H), 10.3 (1H) ppm.

5

Example 3

2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

10

a) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-ol-3-phenylpropan-2-yl)amide

15

1.5 g of intermediate 2b were reacted in 40 ml of DMF with 0.7 ml of triethylamine, 1.0 g of 3-amino-2-hydroxy-4-phenylbutyramide hydrochloride, 0.6 g of HOBT and 0.9 g of EDC in analogy to Example 1c, resulting in 0.8 g (38%) of the product.

20

b) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

25

0.7 g of intermediate 3a were oxidized in 20 ml of DMSO with 0.7 g of SO₃/pyridine complex in the presence of 0.8 g of triethylamine in analogy to Example 1d, resulting in 0.1 g (18%) of the product in the form of the free base.

30

¹H-NMR (d₆-DMSO): δ = 2.3 (4H), 2.8-3.5 (8H), 5.3 (1H), 6.7-7.5 (16H), 7.8 (1H), 8.1 (1H), 10.3 (1H) ppm.

Example 4

35

2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

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- a) Methyl 2-(4-((3-methylphenyl)-1-piperazinyl)-methyl)benzoate [sic]

5 4.0 g of methyl 2-chloromethylbenzoate and 4.4 g of 3-methylphenylpiperazine were heated in 200 ml of DMF in the presence of 4.5 g of potassium carbonate at 140°C for 3 h. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases
10 were washed three times with saturated brine, dried over magnesium sulfate and concentrated, resulting in 6.5 g (92%) of the product.

- b) 2-(4-((3-Methylphenyl)-1-piperazinyl)methyl)-benzoic [sic] acid
15

5.9 g of intermediate 4a were dissolved in 75 ml of THF and hydrolyzed with 0.9 g of LiOH in 75 ml of water in analogy to Example 1b, resulting in
20 2.9 g (51%) of the product.

- c) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)-benzoic acid N-(1-carbamoyl-1-ol-3-phenylpropan-2-yl)amide
25

1.8 g of intermediate 4b were introduced into 50 ml of DMF in the presence of 2.7 ml of triethylamine, and 0.8 g of HOBT, 1.3 g of 3-amino-2-hydroxy-4-phenylbutyramide hydrochloride
30 and 1.2 g of EDC were successively added, in analogy to Example 1c, resulting in 1.4 g (50%) of the product.

- d) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)-benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide
35

1.2 g of intermediate 4c were dissolved in 30 ml of DMSO and oxidized with 1.6 g of SO₃/pyridine

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complex in the presence of 1.5 ml of triethylamine in analogy to Example 1d, resulting in 1.0 g (83%) of the product.

5 MS: m/e = 484 (M^+)

Examples 5 and 6 were synthesized in analogy to Example 1.

10 Example 5

3-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide fumarate

15 $^1\text{H-NMR}$ (d_6 -DMSO): δ = 2.5 (4H), 2.9 (1H), 3.2 (4H), 3.3 (1H), 3.7 (2H), 4.5 (1H), 6.6 (2H), 6.75 (1H), 6.9 (2H), 7.2 (2H), 7.2-7.3 (5H), 7.45 (1H), 7.55 (1H), 7.75 (1H), 7.8 (2H), 8.9 (1H), 9.7 (1H) ppm.

20 Example 6

3-((4-(2-tert-Butyl-4-trifluoromethylpyrimidin-6-yl)-homopiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

25

MS: m/e = 568 ($M^+ + 1$)

Example 7

30 4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)-benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

a) 4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)benzoic acid

35

11.5 g of N-(3,4-dioxomethylene)benzyl-N-methylamine and 15.5 g of triethylamine were introduced into [lacuna], and 15.0 g of 4-bromomethylbenzoic acid in 100 ml of THF were

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added. The reaction mixture was briefly heated to reflux and then stirred at room temperature for 15 h. After filtering off the salts, the mother liquor was concentrated, and the residue was dissolved in ethyl acetate and washed with water. The aqueous phase was made alkaline and extracted several times with ethyl acetate, resulting in 6.6 g (32%) of the product as a white solid.

b) 4-(N-(3,4-Dioxomethylene)benzyl-N-methylamino-methyl)benzoic acid N-(3-phenylpropan-1-ol-2-yl)-amide

4.4 g of intermediate 5a [sic] were introduced into 50 ml of DMF in the presence of 2.9 g of triethylamine, and 1.8 g of HOBT, 2.0 g of phenylalaninol and 2.8 g of EDC were successively added, in analogy to Example 1c, resulting in 2.3 g (40%) of the product.

c) 4-(N-(3,4-Dioxomethylene)benzyl-N-methylamino-methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)-amide

2.0 g of intermediate 5b [sic] were dissolved in 60 ml of DMSO and oxidized with 2.1 g of SO₃/pyridine complex in the presence of 1.8 ml of triethylamine in analogy to Example 1d, resulting in 1.3 g (68%) of the product.

¹H-NMR (CF₃COOD): δ = 2.9 (3H), 3.2 (2H), 4.3-4.9 (5H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.2-7.4 (5H), 7.8 (2H), 8.25 (2H) ppm.

MS: m/e = 430 (M⁺)

Examples 8-28 were prepared in analogy to Example 7.

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Example 8

4-(N-Benzyl-N-methylaminomethyl)benzoic acid N-(3-phenylpropan-1-yl)amide

5

¹H-NMR (CF₃COOD): δ = 2.9 (3H), 3.2 (2H), 4.3-5.0 (5H), 6.7 (1H), 7.25-7.5 (8H), 7.55 (2H), 7.8 (2H), 8.2 (2H) ppm.

10 MS: m/e = 386 (M⁺)**Example 9**

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoic acid N-(3-phenylpropan-1-yl)amide

15

¹H-NMR (CF₃COOD): δ = 2.9 (3H), 3.3 (2H), 4.0 (3H), 4.3-4.9 (5H), 6.7 (1H), 7.1-7.4 (7H), 7.5 (2H), 7.8 (2H), 8.2 (2H) ppm.

20

MS: m/e = 416 (M⁺)**Example 10**

4-(N-Benzyl-N-methylaminomethyl)benzoic acid N-(3-butan-1-yl)amide

25

¹H-NMR (CF₃COOD): δ = 1.1 (3H), 1.6 (2H), 2.0 (2H), 2.9 (3H), 4.3-4.5 (3H), 4.7 (1H), 4.8 (1H), 6.6 (1H), 7.3-7.6 (5H), 7.8 (2H), 8.3 (2H) ppm.

30

MS: m/e = 338 (M⁺)**Example 11**

4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)-benzoic acid N-(3-butan-1-yl)amide

35

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$^1\text{H-NMR}$ (CF_3COOD): δ = 1.1 (3H), 1.6 (2H), 1.9 (2H), 2.9 (3H), 4.25-4.6 (4H), 4.75 (1H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.8 (2H), 8.3 (2H) ppm.

5 MS: m/e = 382 (M^+)

Example 12

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoic acid
10 N-(3-butan-1-al-2-yl)amide

MS: m/e = 368 (M^+)

Example 13

15

4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)-
benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

$^1\text{H-NMR}$ (CF_3COOD): δ = 1.0-2.0 (13H), 2.9 (3H), 4.3-4.9 (4H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.8 (2H), 8.3 (2H)
20 ppm.

MS: m/e = 436 (M^+)

25 Example 14

4-(N-(4-Benzyl-N-methylaminomethyl)benzoic acid N-(3-
cyclohexylpropan-1-al-2-yl)amide

$^1\text{H-NMR}$ (d_6 -DMSO): δ = 1.0-1.8 (13H), 2.1 (3H), 3.4 (2H),
30 3.5 (2H), 4.3 (1H), 7.1-7.4 (5H), 7.5 (2H), 7.8 (2H),
8.8 (1H), 9.5 (1H) ppm.

Example 15

35

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoic acid
N-(3-cyclohexylpropan-1-al-2-yl)amide

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¹H-NMR (CDCl₃): δ = 1.0-1.8 (13H), 2.1 (3H), 3.4 (2H), 3.5 (2H), 3.7 (3H), 4.3 (1H), 6.8 (2H), 7.25 (2H), 7.5 (2H), 7.9 (2H), 8.8 (1H), 9.5 (1H) ppm.

5 **Example 16**

4-((2-Phenylpyrrolid-1-yl)methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

10 MS: m/e = 420 (M⁺)**Example 17**

4-((2-Phenylpyrrolid-1-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

MS: m/e = 364 (M⁺)**Example 18**

20

4-((2-Phenylpyrrolid-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

MS: m/e = 412 (M⁺)

25

Example 19

4-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

30

¹H-NMR (CDCl₃): δ = 1.0-1.9 (13H), 2.0 (2H), 2.8 (2H), 3.3 (2H), 4.5 (2H), 4.8 (1H), 6.4 (1H), 6.5 (2H), 7.0 (2H), 7.4 (2H), 7.8 (2H), 9.7 (1H) ppm.

35 MS: m/e = 404 (M⁺)

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Example 20

4-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

5

¹H-NMR (d₆-DMSO): δ = 1.9 (2H), 2.75 (2H), 2.9 (1H), 3.3 (1H), 3.4 (2H), 4.4 (1H), 4.5 (2H), 6.3 (2H), 6.8 (2H), 7.1-7.25 (5H), 7.3 (2H), 7.7 (2H), 8.8 (1H), 9.5 (1H) ppm.

10

MS: m/e = 398 (M⁺)

Example 21

15 4-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

¹H-NMR (d₆-DMSO): δ = 0.9 (3H), 1.2-2.0 (6H), 2.7 (2H), 3.3 (2H), 4.2 (1H), 4.5 (2H), 6.4 (2H), 6.8 (2H), 7.3 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

20

MS: m/e = 350 (M⁺)

Example 22

25

4-((1,2,3,4-Dihydroisoquinolin-2-yl)methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

¹H-NMR (d₆-DMSO): δ = 0.9-1.8 (13H), 2.7-2.9 (4H), 3.6 (2H), 3.75 (2H), 4.4 (1H), 6.9-7.1 (4H), 7.4 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

30

MS: m/e = 404 (M⁺)

35 **Example 23**

4-((1,2,3,4-Dihydroisoquinolin-2-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

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¹H-NMR (d₆-DMSO): δ = 2.7 (2H), 2.8 (2H), 2.9 (1H), 3.2 (1H), 3.5 (2H), 3.7 (2H), 4.5 (1H), 6.9-7.1 (4H), 7.2-7.3 (5H), 7.5 (2H), 7.75 (2H), 8.8 (1H), 9.5 (1H) ppm.

5

MS: m/e = 398 (M⁺)

Example 24

10 4-((1,2,3,4-Dihydroisoquinolin-2-yl)methyl)benzoic acid
N-(3-butan-1-yl-2-yl)amide hydrochloride

¹H-NMR (d₆-DMSO): δ = 0.9 (3H), 1.2-2.0 (4H), 3.0 (1H), 3.3 (2H), 3.6 (1H), 4.1-4.6 (5H), 7.2 (4H), 7.8 (2H),
15 8.0 (2H), 9.0 (1H), 9.5 (1H), 11.75 (1H) ppm.

Example 25

20 4-((6,7-Dimethoxy-1,2,3,4-dihydroisoquinolin-2-yl)-
methyl)benzoic acid N-(3-cyclohexylpropan-1-yl-2-yl)-
amide

¹H-NMR (d₆-DMSO): δ = 0.9-1.9 (13H), 2.7 (4H), 3.4 (2H), 3.6 (3H), 3.65 (2H), 3.7 (3H), 4.3 (1H), 6.5 (1H), 6.6
25 (1H), 7.5 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 464 (M⁺)

Example 26

30

4-((6,7-Dimethoxy-1,2,3,4-dihydroisoquinolin-2-yl)-
methyl)benzoic acid N-(3-phenylpropan-1-yl-2-yl)amide

¹H-NMR (d₆-DMSO): δ = 2.7 (4H), 2.9 (1H), 3.25 (1H), 3.6
35 (6H), 3.7 (2H), 4.5 (1H), 6.6 (1H), 6.7 (1H), 7.2-7.3
(5H), 7.4 (2H), 7.8 (2H), 8.9 (1H), 9.6 (1H) ppm.

MS: m/e = 458 (M⁺)

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Example 27

4-((6,7-Dimethoxy-1,2,3,4-dihydroisoquinolin-2-yl)-methyl)benzoic acid N-(3-butan-1-yl-2-yl)amide

5

¹H-NMR (d₆-DMSO): δ = 0.9 (3H), 1.4 (2H), 1.5-1.8 (2H), 2.7 (4H), 3.4 (2H), 3.7 (3H), 3.75 (3H), 3.8 (2H), 4.3 (1H), 6.6 (1H), 6.7 (1H), 7.4 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

10

MS: m/e = 410 (M⁺)

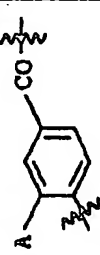


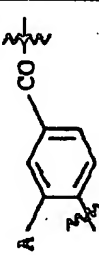


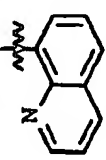
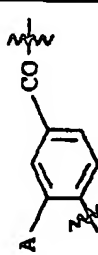
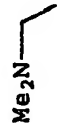

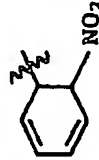
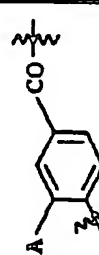


Example 28

15 2-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-butan-1-yl-2-yl)amide

MS: m/e = 441 (M⁺)

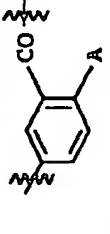
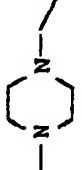

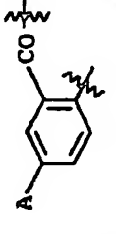


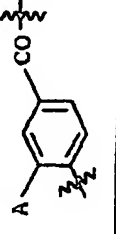


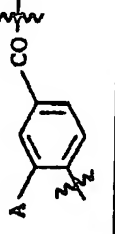
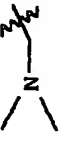
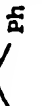
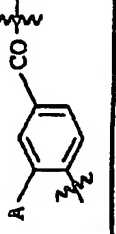
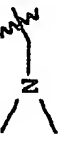
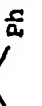
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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^4 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
1	Bu	SO ₂ NH	H				H
2	2-Py	SO ₂ NH	H				H
3		SO ₂ NH	H				H
4		SO ₂ NH	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{R}^4 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
5	Ph	CH ₂ O	H				H
6	2-Py	CH ₂ O	H				H
7	Bu	SO ₂ NH	H				H
8	Naphth	SO ₂ NH	H				H
9	Naphth	SO ₂ NH	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} \quad \text{B} \\ \diagup \quad \diagdown \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^4 \end{array} $	R ³ — (CH ₂) _x —	R ⁶	R ⁵
10	Ph	SO ₂ NH	H				H
11	Bu	SO ₂ NH	H				CONH ₂
12	Naphth	SO ₂ NH	H				CONH ₂
13	Ph	-O-	H				H
14	Ph	-S-	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \parallel \\ \text{A} - \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{B} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
15	2-Py	SO ₂ NH	H				CONH ₂
16	2-Py	SO ₂ NH	H				H
17		SO ₂ NH	H				H
18	Ph	-O-	H				H
19	Ph	-S-	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \\ \\ \text{A} - \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{C}(=\text{O}) - \text{R}^5 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
20	Bu	SO ₂ NH	H				CONH ₂
21	Naphth	SO ₂ NH	H				H
22	Ph	SO ₂ NH	H				H
23	Bu	SO ₂ NH	H				CONH ₂
24	2-Py	SO ₂ NH	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{R}^5 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
25	Ph	-O-	H				CONH ₂
26	2-Py	SO ₂ NH	H				H
27	Ph	-O-	H				CONH ₂
28	Ph	-O-	H				H
29	Naphth	SO ₂ NH	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{C} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
30	Bu	SO ₂ NH	H				H
31	2-Py	SO ₂ NH	H				CONH ₂
32	Ph	-O-	H		Et ₂ N		H
33		SO ₂ NH	H				CONH ₂
34		SO ₂ NH	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^3 - (\text{CH}_2)_x - \\ \\ \text{A} - \text{B} - \text{C} \\ \quad \quad \\ \text{R}^3 \quad \text{O} \quad \text{R}^2 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
35	Ph	-O-	H		Et ₂ N—CH ₂ —	CH ₂ CH ₂ CH ₂ CH ₂ CONH ₂	CONH ₂
36	Ph	-O-	H		Et ₂ N—CH ₂ —	CH ₂ CH ₂ CH ₂ CH ₂ CONH ₂	CONH ₂
37		SO ₂ NH	H			CH ₂ CH ₂ CH ₂ CH ₂ CONH ₂	CONH ₂
38	Ph	CONH	MeO		Me ₂ N—CH ₂ —	CH ₂ CH ₂ CH ₂ CH ₂ CONH ₂	CONH ₂
39	Naphth	CONH	MeO		Et ₂ N—CH ₂ —	CH ₂ CH ₂ CH ₂ CH ₂ CONH ₂	CONH ₂

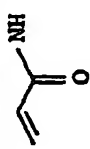

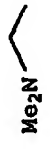
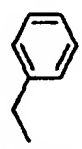
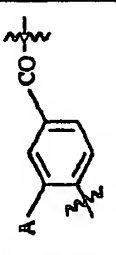


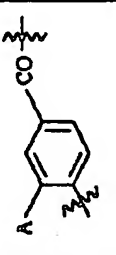

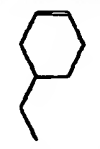
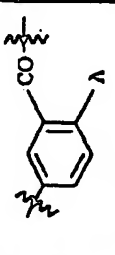
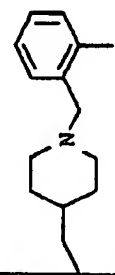
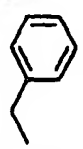

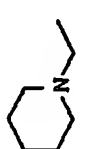

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^3 - (\text{CH}_2)_x \\ \\ \text{A} - \text{B} \\ \quad \\ \text{R}^2 \quad \text{O} \\ \text{C} = \text{O} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
40	Ph	CONH	Et		Me ₂ N — CH ₂ —		H
41	Bu	SO ₂ NH	H				H
42	Naphth	CONH	Et		Et ₂ N — CH ₂ —		H
43	Ph		Et		Me ₂ N — CH ₂ —		H
44		SO ₂ NH	H		Et ₂ N — CH ₂ —		CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} \quad \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{B} - (\text{CH}_2)_x - \text{B} - \text{R}^3 \end{array} $	R ³ — (CH ₂) _x —	R ⁶	R ⁵
45	Ph		MeO		Me ₂ N — 		H
46	Bu	SO ₂ NH	H				CONH ₂
47	Naphth	SO ₂ NH	H				H
48	H	M=O=O	H				H
49	Ph	-O-	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^5 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
50	Ph	·O-	H		Me ₂ N — CH ₂ —		CONH ₂
51	Naphth	CONH	MeO				CONH ₂
52	Bu	SO ₂ NH	H				
53	Ph	SO ₂ NH	H				CONH ₂
54	2-Py	SO ₂ NH	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{R}^4 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
55	Ph	CONH	MeO				CONH ₂
56	Bu	SO ₂ NH	H				H
57		SO ₂ NH	H		Me ₂ N		CONH ₂
58		SO ₂ NH	H				H
59		SO ₂ NH	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁶	R ⁵
60	Ph	CONH	Et				CONH ₂
61	Ph	O—	H				H
62	Ph	O—	H				H
63	Ph	O—	H				CONH ₂
64	Ph	O—	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{C} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
65	Ph	CONH	MeO				CONH ₂
66	Ph	SO ₂ NH	H				
67	Ph	SO ₂ NH	H				CONH ₂
68	Ph	SO ₂ NH	H				H
69	Bu	SO ₂ NH	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} \quad \text{B} \\ \quad / \quad \backslash \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
70		SO ₂ NH	H				H
71		SO ₂ NH	H				CONH ₂
72	Ph	CONH	Et				H
73	Bu	SO ₂ NH	H				CONH—
74	Ph	SO ₂ NH	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{C} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
75	Naphtha	SO ₂ NH	H				H
76		SO ₂ NH	H				H
77		SO ₂ NH	H				CONH ₂
78		SO ₂ NH	H				CONH ₂
79		SO ₂ NH	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \\ \\ \text{A} \text{---} \text{B} \text{---} \text{C} \\ \quad \quad \\ \text{R}^2 \quad \text{O} \quad \text{R}^3 \end{array} $	R ³ ---(CH ₂) _x ---	R ⁴	R ⁵
80	Naphth	CONH	MeO				H
81	Naphth	SO ₂ NH	H				CONH ₂
82	Naphth	SO ₂ NH	H				H
83		SO ₂ NH	H				CONH ₂
84		SO ₂ NH	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \\ \text{O} \\ \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \text{B} \text{---} \text{C} \text{---} \\ \quad \\ \text{A} \quad \text{R}^3 \end{array} $	R ³ --- (CH ₂) _x ---	R ⁴	R ⁵
85	Ph		H				CONH ₂
86	Ph		H				H
87	Ph		H				H
88	Ph		H				CONH ₂
89	Ph	SO ₂ NH	H				CONH ₂

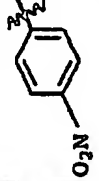
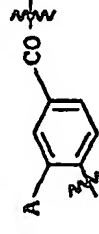
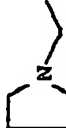

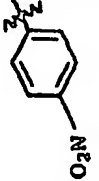
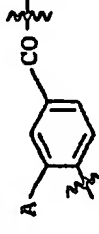
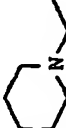

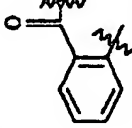
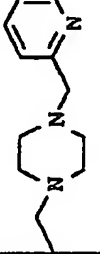


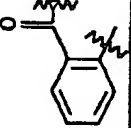
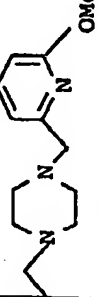

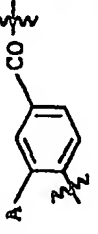
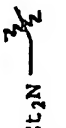
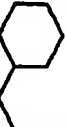
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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \\ \\ \text{A} \text{---} \text{B} \text{---} \\ \quad \\ \text{O} \quad \text{O} \\ \text{C} \quad \text{C} \\ \text{R}^3 \quad \text{R}^3 \end{array} $	R ³ --- (CH ₂) _x ---	R ⁴	R ⁵
90	Naphth	SO ₂ NH	H				H
91	2-Py	SO ₂ NH	H				H
92	2-Py	SO ₂ NH	H				CONH ₂
93		SO ₂ NH	H				CONH ₂
94		SO ₂ NH	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
95		SO ₂ NH	H				CONH ₂
96		SO ₂ NH	H				H
97	H	m=O=O	H				
98	H	m=O=O	H				CONH ₂
99	Bu	SO ₂ NH	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} \quad \text{B} \\ \diagup \quad \diagdown \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
100	Ph	SO ₂ NH	H				H
101	2-Py	SO ₂ NH	H				CONH ₂
102	H	m=O=O	H				H
103	H	m=O=O	H				H
104	Bu	SO ₂ NH	H				

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} \quad \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁶	R ⁵
105	Ph	SO ₂ NH	H				H
106	2-Py	SO ₂ NH	H				CONH ₂
107	H	m=O=O	H				CONH ₂
108	H	m=O=O	H				CONH ₂
109	H	m=O=O	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} \quad \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
110	H	m=O=O	H			H	
111	Ph	SO ₂ NH	H			Ph	
112	Ph	SO ₂ NH	H			Ph	CONH ₂
113	2-Py	SO ₂ NH	H				H
114		SO ₂ NH	H				CONH ₂

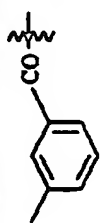
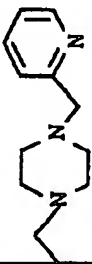




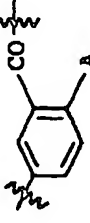
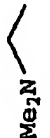
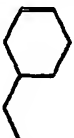
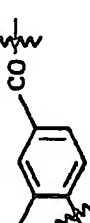



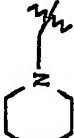

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^4 - (\text{CH}_2)_x \end{array} $	R ³ - (CH ₂) _x	R ⁴	R ⁵
115		SO ₂ NH	H		Et ₂ N -		H
116	H	m=O=O	H				H
117	H	m=O=O	H				H
118	Ph	SO ₂ NH	H				H
119	Naphth	SO ₂ NH	H				CONH ₂

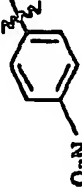
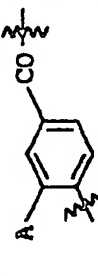
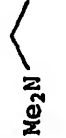

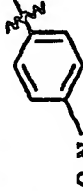
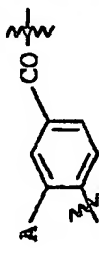



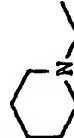


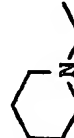
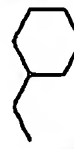
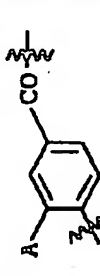
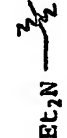

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^4 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
120	H	SONH ₂	H				H
121	Ph	-O-	H				H
122	Ph	-O-	H				H
123	Ph	SO ₂ NH	H				H
124	Naphth	SO ₂ NH	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \quad // \\ \text{A} - \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
125		SO ₂ NH	H				H
126		SO ₂ NH	H				CONH ₂
127	Ph	S—	H				CONH ₂
128	Ph	S—	H				CONH ₂
129	Bu	SO ₂ NH	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{R}^4 \end{array} $	R ³ --- (CH ₂) _x ---	R ⁴	R ⁵
130	Ph	SO ₂ NH	H				CONH ₂
131		SO ₂ NH	H				CONH ₂
132		M=O=O	H				CONH ₂
133	Ph	CH ₂ O	H				CONH ₂
134	2-Py	CH ₂ O	H				CONH ₂





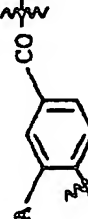
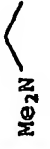
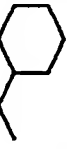
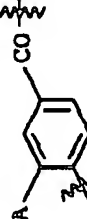
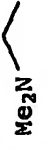

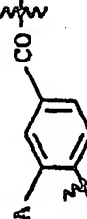


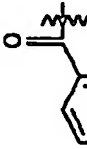
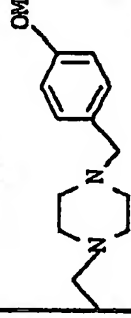
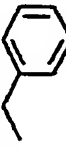
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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^5 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
135	3-Py	CH ₂ O	H		Me ₂ N—CH ₂ —	—CH ₂ —Ph	CONH ₂
136	4-Py	CH ₂ O	H			—CH ₂ —Ph	H
137	2-Tol	CH ₂ O	H		Me ₂ N—CH ₂ —	—CH ₂ —Ph	H
138	3-Tol	CH ₂ O	H		Et ₂ N—CH ₂ —	—CH ₂ —CH ₂ —CH ₂ —	H
139		CH ₂ O	H		Me ₂ N—CH ₂ —	—CH ₂ —Cyclohexyl	CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{R}^3 \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
140		CH ₂ O	H				H
141	Ph	CONH ₂	H				CONH ₂
142	Naphth	CONH ₂	H				CONH ₂
143	Naphth	CONH ₂	H				CONH ₂
144	H	m=O=O	H				CONH ₂

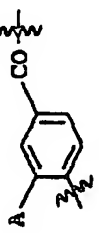

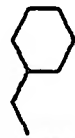
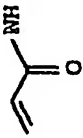
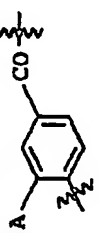
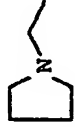

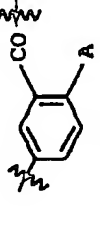
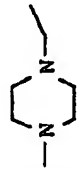

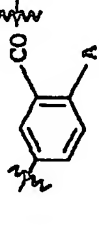
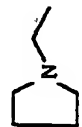

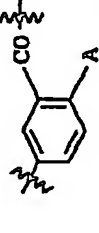
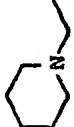
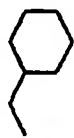
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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{R}^4 \end{array} $	R ³ — (CH ₂) _x —	R ^d	R ⁵
145	2-Py	CH ₃ O	H		Me ₂ N —	Ph	H
146	3-Py	CH ₃ O	H		Et ₂ N —		CONH ₂
147		CH ₃ O	H			Ph	H
148	H	NO ₂	H			Ph	H
149	Ph	CONH	H				H

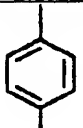
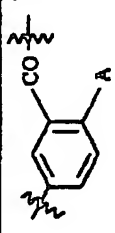
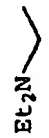

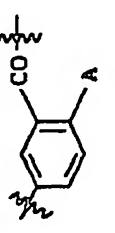


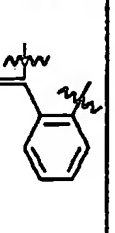


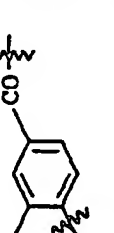

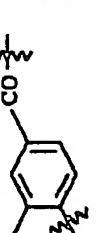
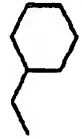
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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{R}^3 \\ \quad \\ \text{---} (\text{CH}_2)_x \text{---} \end{array} $	R ³ --- (CH ₂) _x ---	R ⁴	R ⁵
150	Naphth	CONH	H				H
151	Ph		H				H
152	4-Py	CH ₂ O	H				CONH ₂
153	2-Tol	CH ₂ O	H				H
154	3-Tol	CH ₂ O	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{C} - \text{C} \\ \parallel \\ \text{O} \end{array} $	R ³ — (CH ₂) _x —	R ⁶	R ⁵
155		CH ₂ O	H				H
156	Ph	CH ₂ O	H				CONH ₂
157	H	m=O=O	H				CONH ₂
158	Naphth	CONH	H		Me ₂ N		H
159	Ph	CONH	H		Me ₂ N		CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
160	H	R=O=O	H				H
161	Ph	CH ₂ O	H				H
162	2-Py	CH ₂ O	H				H
163	2-Tol	CH ₂ O	H				CONH ₂
164	3-Py	CH ₂ O	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^5 \end{array} $	R ³ — (CH ₂) _x —	R ⁶	R ⁵
165	3-Tol	CH ₂ O	H		Et ₂ N —		CONH ₂
166		CH ₂ O	H		Me ₂ N —		H
167		CH ₂ O	H				H
168	4-Py	CH ₂ O	H		Et ₂ N —		CONH ₂
169	Ph	SO ₂ NH	MeO				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^3 - (\text{CH}_2)_x - \text{B} - \text{C}(=\text{O}) - \text{R}^2 \\ \quad \\ \text{A} \quad \text{B} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
170	Naphth	SO ₂ NH	MeO		Me ₂ N—	Ph	H
171	3-Tol	CH ₂ O	H		Me ₂ N—		CONH ₂
172	ph	CONH	H				H
173	Naphth	CONH	H				H
174	Bu	SO ₂ NH	Et		Et ₂ N—		CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{---} \text{O} \\ \text{A} \text{---} \text{B} \text{---} \text{C} \\ \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \end{array} $	R ³ ---(CH ₂) _x ---	R ⁴	R ⁵
175	3-Tol	CH ₃ O	H		Et ₂ N		H
176	3-Tol	CH ₃ O	H		Et ₂ N		CONH ₂
177	4-Py	CH ₃ O	H				H
178	4-Py	CH ₃ O	H				H
179	Ph	CH ₃ O	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{R}^3 - (\text{CH}_2)_x - \\ \parallel \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
180	Ph	CH ₂ O	H				CONH ₂
181	H	m=O=O	H				CONH ₂
182	Ph	CH ₂ O	H				CONH ₂
183	2-Py	CH ₂ O	H				H
184	MeO-Ph	CH ₂ O	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^4 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
185	Ph	CONH	H		Me ₂ N —		CONH ₂
186	Naphth	CONH	H		Me ₂ N —		H
187	Ph		H		Me ₂ N —		H
188	3-Py	CH ₂ O	H		Et ₂ N —		H
189	3-Tol	CH ₃ O	H		Me ₂ N —		H

No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \diagup \quad \diagdown \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^4 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x	R ⁴	R ⁵
190	4-Py	CH ₂ O	H				CONH ₂
191	2-Tol	CH ₂ O	H				CONH ₂
192		CH ₂ O	H				H
193	H	m=O=O	H				H
194	Ph	CONH	H				CONH ₂










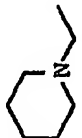



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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \\ \diagup \quad \diagdown \\ \text{A} \quad \text{B} \\ \diagdown \quad \diagup \\ \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \end{array} $	R ³ ---(CH ₂) _x ---	R ⁴	R ⁵
195	Naphth	CONH	H				CONH ₂
196	H	m=O=O	H				CONH ₂
197	2-Py	CH ₂ O	H				H
198	3-Py	CH ₂ O	H				CONH ₂
199	3-Tol	CH ₂ O	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^5 \end{array} $	R ³ — (CH ₂) _x —	R ⁶	R ⁵
200	Ph	CH ₂ O	H		Et ₂ N—		H
201		CH ₂ O	H		Me ₂ N—		CONH ₂
202	4-Py	CH ₂ O	H		Me ₂ N—		H
203		CH ₂ O	H				CONH ₂
204	2-Py	CH ₂ O	H		Me ₂ N—		CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \\ \parallel \\ \text{R}^3 - (\text{CH}_2)_x - \text{B} - \text{C} - \text{R}^1 \\ \diagup \quad \diagdown \\ \text{A} \quad \text{A} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
205	Ph	CH ₂ O	H				H
206	2-Py	CH ₂ O	H				CONH ₂
207	2-Tol	CH ₃ O	H				H
208	Ph	CONH	H				H
209	Naphth	CONH	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^1 - (\text{CH}_2)_x \quad \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
210	3-Py	CH ₂ O	H		Me ₂ N—CH ₂ —	Ph	H
211	4-Py	CH ₂ O	H				H
212	MeO—C ₆ H ₄	CH ₂ O	H		Et ₂ N—CH ₂ —		CONH ₂
213	Ph		H		Me ₂ N—CH ₂ —		CONH ₂
214	Ph	CONH	H		Me ₂ N—CH ₂ —		CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^5 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
215		CH ₂ O	H				CONH ₂
216	3-Tol	CH ₂ O	H				H
217	H	m=O=O	H				CONH ₂
218	H	m=O=O	H				H
219	2-Py	CH ₂ O	H				H

No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{R}^3 - (\text{CH}_2)_x - \text{A} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
220	3-Py	CH ₂ O	H				H
221	2-Tol	CH ₂ O	H				CONH ₂
222	4-Tol	CH ₂ O	H				CONH ₂
223	4-Py	CH ₂ O	H				CONH ₂
224		CH ₂ O	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
225	4-Py	CH ₂ O	H		Et ₂ N—	Ph	H
226	Ph	CH ₂ O	H				CONH ₂
227	3-Tol	CH ₂ O	H		Me ₂ N—		H
228		CH ₂ O	H				H
229	H	m=O=O	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} \quad \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁶	R ⁵
230	Ph	CONH	H				CONH ₂
231	Naphth	CONH	H				CONH ₂
232	2-Tol	CH ₂ O	H				H
233	2-Tol	CH ₂ O	H				CONH ₂
234	3-Py	CH ₃ O	H				H

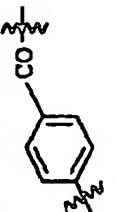
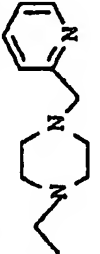
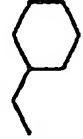

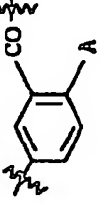




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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{C} - \text{O} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
235	Ph	CH ₂ O	H				CONH ₂
236		CH ₂ O	H				H
237		CH ₂ O	H				H
238		CH ₂ O	H				H
239		CH ₂ O	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
240	H	M=O=O	H				
241	Ph	CH ₃ O	H		Me ₂ N—	Ph	H
242	3-Py	CH ₃ O	H		Me ₂ N—	Ph	CONH ₂
243	4-Py	CH ₃ O	H			Ph	H
244	2-Tol	CH ₃ O	H		Et ₂ N—	Ph	H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{---} \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
245	3-Tol	CH ₂ O	H				CONH ₂
246		CH ₂ O	H				H
247		CH ₂ O	H				H
248	2-Py	CH ₂ O	H				CONH ₂
249	Ph	CONH	H				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{R}^5 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
250	Ph	CONH	H			Ph	CONH ₂
251	Ph	CONH	H				H
252	Naphth	CONH	H				H
253	Ph	SO ₂ NH	Et				H
254	Ph	CH ₂ O	H				H









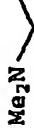

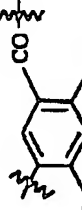
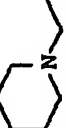




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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \quad // \\ \text{A} \quad \text{B} \\ \quad \\ \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \end{array} $	R ³ ---(CH ₂) _x ---	R ⁴	R ⁵
255	2-Py	CH ₂ O	H				CONH ₂
256	MeO-C ₆ H ₄	CH ₂ O	H				H
257	3-Py	CH ₂ O	H				CONH ₂
258	2-Tol	CH ₂ O	H				CONH ₂
259	3-Tol	CH ₂ O	H				CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{C} - \text{R}^4 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
260		CH ₃ O	H				H
261	4-Py	CH ₃ O	H				CONH ₂
262	Ph	CH ₃ O	H				H
263	Bu	SO ₂ NH	MeO				H
264	Naphth	SO ₂ NH	Et				H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \\ \diagup \quad \diagdown \\ \text{A} \quad \text{B} \\ \quad \quad \quad \text{O} \\ \quad \quad \quad \parallel \\ \quad \quad \quad \text{---} \end{array} $	R ³ ---(CH ₂) _x ---	R ⁴	R ⁵
265	4-Py	CH ₂ O	H		Et ₂ N-CH ₂ -		CONH ₂
266	3-Tol	CH ₂ O	H				H
267	Ph	CONH	H		Et ₂ N-CH ₂ -		CONH ₂
268	Ph		H		Et ₂ N-CH ₂ -		CONH ₂
269	2-Py	CH ₂ O	H				CONH ₂


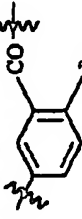
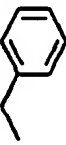
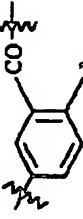

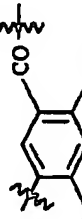
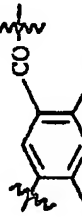

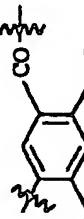
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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{R}^3 \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
270	2-Tol	CH ₃ O	H		Et ₂ N —	— Ph	CONH ₂
271	Ph	CH ₃ O	H		Me ₂ N —	—	H
272	3-Py	CH ₃ O	H			— Ph	CONH ₂
273		CH ₂ O	H			— Ph	CONH ₂
274	Ph	SO ₂ NH	Et		Et ₂ N —	— Ph	H


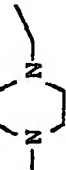









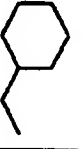
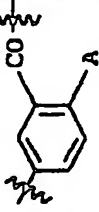
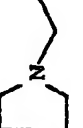

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \quad \text{O} \\ \quad // \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x - \text{R}^4 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
275		CH ₂ O	H		Et ₂ N —		CONH ₂
276	Naphth	SO ₂ NH	Et		Me ₂ N —		CONH ₂
277	Ph	SO ₂ NH	MeO		Me ₂ N —	Ph	H
278	Naphth	SO ₂ NH	MeO			Ph	H
279	Bu	SO ₂ NH	MeO		Me ₂ N —	Ph	H

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \\ \text{A} \quad \text{B} \\ \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \end{array} $	R ³ ---(CH ₂) _x ---	R ⁴	R ⁵
280	Ph	CH ₃ O	H				CONH ₂
281		CH ₂ O	H		Et ₂ N		H
282	Ph	CH ₂ O	H		Me ₂ N		CONH ₂
283		CH ₂ O	H				H
284	2-Py	CH ₃ O	H				H

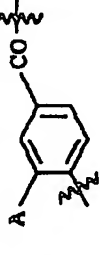


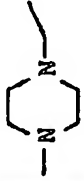
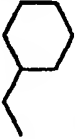




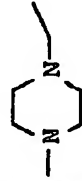


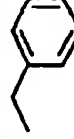
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No	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \\ \\ \text{B} \\ \\ \text{A} \\ \\ \text{R}^3 - (\text{CH}_2)_x \end{array} $	R ³ - (CH ₂) _x	R ⁴	R ⁵
285	2-Py	CH ₂ O	H		Et ₂ N		CONH ₂
286	3-Py	CH ₂ O	H			Ph	H
287		CH ₂ O	H			Ph	CONH ₂
288	2-Tol	CH ₂ O	H				H
289	Ph		H		Et ₂ N		CONH ₂

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^3 \text{---} (\text{CH}_2)_x \text{---} \\ \\ \text{A} \text{---} \text{B} \text{---} \\ \quad \\ \text{R}^2 \quad \text{O} \\ \text{C} \end{array} $	R ³ ---(CH ₂) _x ---	R ⁴	R ⁵
290	Ph	CONH	H		Et ₂ N---		CONH ₂
291	4-Py	CH ₂ O	H				H
292	4-Py	CH ₂ O	H				CONH ₂
293	3-Tol	CH ₂ O	H				CONH ₂
294	2-Tol	CH ₂ O	H		Et ₂ N---		CONH ₂


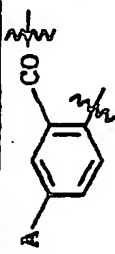
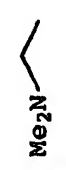


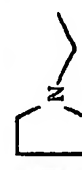

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No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{R}^3 \\ \quad \\ \text{---} (\text{CH}_2)_x \text{---} \end{array} $	R ³ --- (CH ₂) _x ---	R ⁴	R ⁵
295 H		m=O=O	H				H
296 H		m=O=O	H				H
297 3-Tol		CH ₂ O	H				H
298 2-Py		CH ₂ O	H				H

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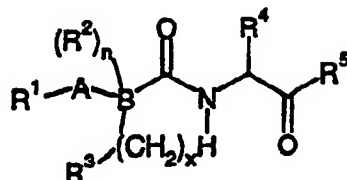
No.	R ¹	A	R ²	$ \begin{array}{c} \text{R}^2 \text{ O} \\ \parallel \\ \text{A} - \text{B} - \text{C} \\ \quad \\ \text{R}^3 - (\text{CH}_2)_x \quad \text{R}^5 \end{array} $	R ³ — (CH ₂) _x —	R ⁴	R ⁵
299	 MeO	CH ₂ O	H		 Me ₂ N		CONH ₂
298	2-Tol	CH ₂ O	H				H

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We claim:

1. An amide of the formula I



5

and its tautomeric and isomeric forms, possible enantiomeric and diastereomeric forms, and possible physiologically tolerated salts, in which the variables have the following meanings:

R^1 can be hydrogen, C_1 - C_6 -alkyl, branched and unbranched, phenyl, naphthyl, quinolyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinazolyl, quinoxalyl, thienyl, benzo-thienyl, benzofuranyl, furanyl and indolyl, it being possible for the rings also to be substituted by to 3 R^6 radicals, and

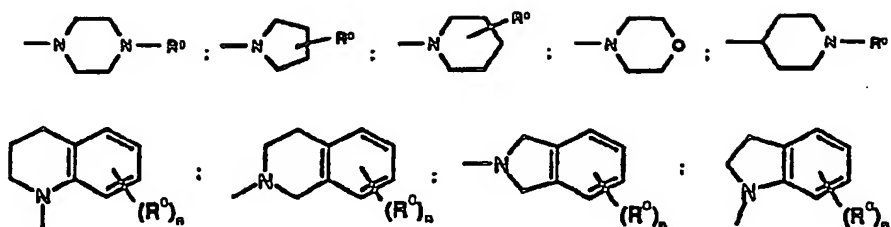
R^2 are hydrogen, C_1 - C_6 -alkyl, branched or unbranched, O - C_1 - C_6 -alkyl, branched or unbranched, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_1 - C_6 -alkyl-phenyl, C_2 - C_6 -alkenyl-phenyl, C_2 - C_6 -alkynyl-phenyl, OH, Cl, F, Br, I, CF_3 , NO_2 , NH_2 , CN, COOH, COO - C_1 - C_4 -alkyl, $NHCO$ - C_1 - C_4 -alkyl, $NHCO$ -phenyl, $CONHR^9$, $NHSO_2$ - C_1 - C_4 -alkyl, $NHSO_2$ -phenyl, SO_2 - C_1 - C_4 -alkyl and SO_2 -phenyl, and

R^3 can be NR^7R^8 or a ring such as

30

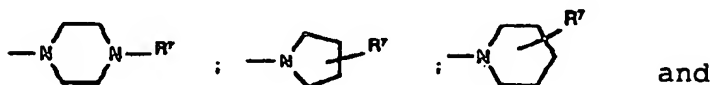
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5 R^4 is $-C_1-C_6$ -alkyl, branched or unbranched, which may also carry a phenyl, pyridyl, thienyl, cyclohexyl, indolyl or naphthyl ring which is in turn substituted by a maximum of two R^6 radicals, and

10 R^5 is hydrogen, $COOR^{11}$ and $CO-Z$ in which Z is $NR^{12}R^{13}$ and



15 R^6 is hydrogen, C_1-C_4 -alkyl, branched or unbranched, $-O-C_1-C_4$ -alkyl, OH, Cl, F, Br, I, CF_3 , NO_2 , NH_2 , CN, $COOH$, $COO-C_1-C_4$ -alkyl, $-NHCO-C_1-C_4$ -alkyl, $-NHCO$ -phenyl, $-NHSO_2-C_1-C_4$ -alkyl, $-NHSO_2$ -phenyl, $-SO_2-C_1-C_4$ -alkyl and $-SO_2$ -phenyl, and

20 R^7 is hydrogen, C_1-C_6 -alkyl, linear or branched, and which may be substituted by a phenyl ring which itself may also be substituted by one or two R^{10} radicals, and

25 R^8 is hydrogen, C_1-C_6 -alkyl, linear or branched, which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

30 R^9 is hydrogen, C_1-C_6 -alkyl, branched or unbranched, which may also carry a sub-

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stituent R^{16} , or phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, naphthyl, quinolyl, imidazolyl, which may also carry one or two substituents R^{14} , and

5

R^{10} can be hydrogen, C_1 - C_4 -alkyl, branched or unbranched, $-O$ - C_1 - C_4 -alkyl, OH, Cl, F, Br, I, CF_3 , NO_2 , NH_2 , CN, COOH, COO - C_1 - C_4 -alkyl, $-NHCO$ - C_1 - C_4 -alkyl, $-NHCO$ -phenyl, $-NHSO_2$ - C_1 - C_4 -alkyl, $-NHSO_2$ -phenyl, $-SO_2$ - C_1 - C_4 -alkyl and $-SO_2$ -phenyl

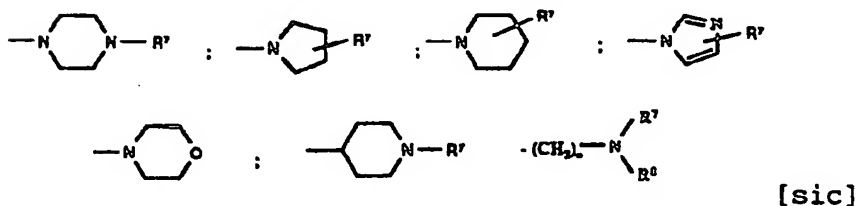
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R^{11} is hydrogen, C_1 - C_6 -alkyl, linear or branched, and which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

15

R^{12} is hydrogen, C_1 - C_6 -alkyl, branched and unbranched, and

20



R^{13} is hydrogen, C_1 - C_6 -alkyl, branched or unbranched, which may also be substituted by a phenyl ring which may also carry an R^{10} radical, and by [lacuna] and

25

R^{14} is hydrogen, C_1 - C_6 -alkyl, branched or unbranched, O - C_1 - C_6 -alkyl, branched or unbranched, OH, Cl, F, Br, I, CF_3 , NO_2 , NH_2 , CN, COOH, COO - C_1 - C_4 -alkyl, or two R^{14} radicals may represent a bridge $OC(R^{15})_2O$, and

30

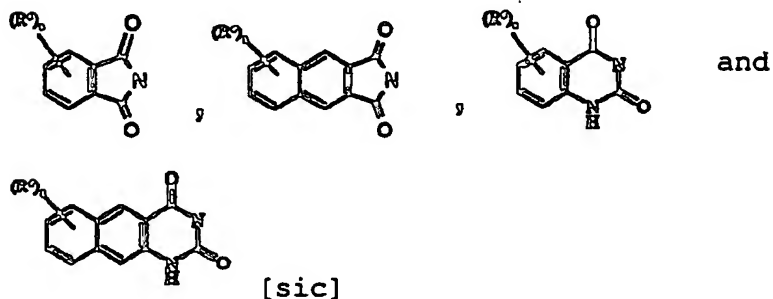
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R^{15} is hydrogen, C_1 - C_6 -alkyl, branched and unbranched, and

R^{16} can be a phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, pyrrolyl, naphthyl, quinolyl, imidazolyl ring, which may also carry one or two substituents R^6 , and

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$,
 $-(CH_2)_o-S-(CH_2)_m-$, $-(CH_2)_o-SO-(CH_2)_m-$,
 $-(CH_2)_o-SO_2-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$,
 $-CO-CH=CH-$, $-(CH_2)_o-CO-(CH_2)_m-$,
 $-(CH_2)_m-NHCO-(CH_2)_o-$, $-(CH_2)_m-CONH-(CH_2)_o-$,
 $-(CH_2)_m-NHSO_2-(CH_2)_o-$, $-NH-CO-CH=CH-$,
 $-(CH_2)_m-SO_2NH-(CH_2)_o-$, $-CH=CH-CONH-$ and



R^1 -A together are also
 [lacuna]
 and

B is phenyl, pyridine, pyrimidine, pyrazine, imidazole and thiazole, and

x is 1, 2 or 3, and

n is a number 0, 1 or 2, and

m, o is, independently of one another, a number 0, 1, 2, 3 or 4.

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2. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where
- 5 B is pyridine or phenyl, and
- R⁵ is hydrogen, and
- 10 R⁹ hydrogen, C₁-C₆-alkyl, branched or unbranched, which [lacuna] also carry a substituent R¹⁶,
- R¹⁶ phenyl which may also carry one or two substituents R¹⁴, and
- 15 n 0 and 1, and
- x 1.
3. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where
- 20 B is pyridine or phenyl, and
- R⁵ is CONR¹²R¹³, and
- 25 R⁹ hydrogen, C₁-C₆-alkyl, branched or unbranched, which [lacuna] also carry a substituent R¹⁶,
- 30 R¹⁶ phenyl which may also carry one or two substituents R¹⁴, and
- n 0 and 1, and
- x 1.
- 35 4. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where
- B is pyridine or phenyl, and

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R^2 is hydrogen

R^5 is hydrogen, and

5

R^9 hydrogen, C_1 - C_6 -alkyl, branched or unbranched,
which [lacuna] also carry a substituent R^{16} ,

10

R^{16} phenyl which may also carry one or two sub-
stituents R^{14} , and

n 0 and 1, and

x 1.

15

5. An amide with heterocyclic substituents, of the
formula I, as claimed in claim 1, where

20

B is pyridine or phenyl, and

R^2 is hydrogen

R^5 is $CONR^{12}R^{13}$, and

25

R^9 hydrogen, C_1 - C_6 -alkyl, branched or unbranched,
which [lacuna] also carry a substituent R^{16} ,

R^{16} phenyl which may also carry one or two sub-
stituents R^{14} , and

30

n 0 and 1, and

x 1.

- 35 6. An amide with heterocyclic substituents, of the
formula I, as claimed in claim 1, where

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$,
 $-(CH_2)_o-S-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$,

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$-(CH_2)_m-CONH-(CH_2)_o-$,
 $-(CH_2)_m-SO_2NH-(CH_2)_o-$, and

5 B is pyridine or phenyl, and

R^2 is hydrogen, and

R^5 is hydrogen, and

10 R^9 hydrogen, C_1-C_6 -alkyl, branched or
unbranched, which may also carry a sub-
stituent R^{16} , and

15 R^{16} phenyl, and

m, n, o 0 and 1, and

x 1.

20 7. An amide with heterocyclic substituents, of the
formula I, as claimed in claim 1, where

25 A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$,
 $-(CH_2)_o-S-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$,
 $-(CH_2)_m-CONH-(CH_2)_o-$,
 $-(CH_2)_m-SO_2NH-(CH_2)_o-$, and

B is pyridine or phenyl, and

30 R^2 is hydrogen

R^5 is $CONR^{12}R^{13}$, and

35 R^9 hydrogen, C_1-C_6 -alkyl, branched or
unbranched, which may also carry a sub-
stituent R^{16} , and

R^{16} phenyl, and

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m, n, o 0 and 1, and

x 1.

5

8. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

10

R¹, R² are hydrogen, and

R⁵ is hydrogen, and

15

R⁹ hydrogen, C₁-C₆-alkyl, branched or unbranched, which may also carry a substituent R¹⁶, and

R¹⁶ phenyl, and

20

m, n, o 0, and

x 1.

- 25 9. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

30

R¹, R² are hydrogen

R⁵ is CONR¹²R¹³, and

35

R⁹ hydrogen, C₁-C₆-alkyl, branched or unbranched, which may also carry a substituent R¹⁶, and

R¹⁶ phenyl, and

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m, n, o 0

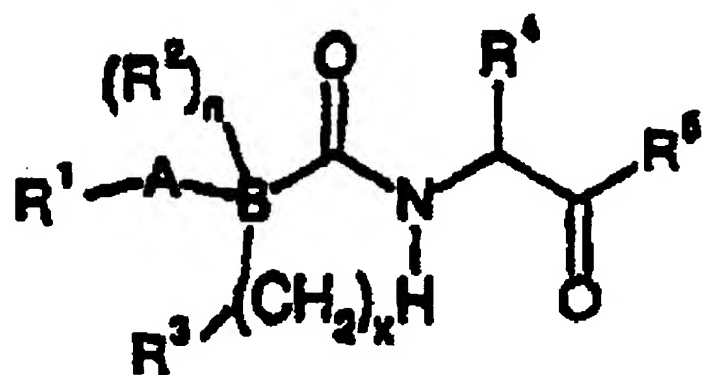
x 1.

- 5 10. The use of amides of the formula I as claimed in claims 1-5 for treating diseases.
11. The use of amides of the formula I as claimed in claims 1-5 as inhibitors of cysteine proteases.
- 10 12. The use as claimed in claim 6 as inhibitors of cysteine proteases such as calpains and cathepsins, in particular calpains I and II and cathepsins B and L.
- 15 13. The use of amides of the formula I as claimed in claims 1-5 for production as pharmaceuticals for treating diseases in which elevated calpain activities occur.
- 20 14. The use of amides of the formula I as claimed in claims 1-5 for producing pharmaceuticals for treating neurodegenerative disorders and neuronal damage.
- 25 15. The use as claimed in claim 9 for treating neurodegenerative disorders and neuronal damage induced by ischemia, trauma or massive bleeding.
- 30 16. The use as claimed in claim 10 for treating stroke and craniocerebral trauma.
17. The use as claimed in claim 10 for treating Alzheimer's disease and Huntington's disease.
- 35 18. The use as claimed in claim 10 for treating epilepsies.

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19. The use of compounds of the formula I as claimed in claims 1-5 for producing pharmaceuticals and [sic] treating damage to the heart after cardiac ischemias, damage to the kidneys after renal ischemias, skeletal muscle damage, muscular dystrophies, damage produced by proliferation of smooth muscle cells, coronary vasospasm, cerebral vasospasm, cataracts of the eyes and restenosis of blood vessels after angioplasty.
20. The use of amides of the formula I as claimed in claims 1-5 for producing pharmaceuticals for treating tumors and metastasis thereof.
21. The use of amides of the formula I as claimed in claims 1-5 for producing pharmaceuticals for treating disorders in which elevated interleukin-1 levels occur.
22. The use of amides according to claims 1-5 for treating immunological disorders such as inflammations and rheumatic disorders.
23. A pharmaceutical preparation for oral, parenteral or intraperitoneal use, comprising at least one amide I as claimed in claims 1-5 per single dose, besides conventional pharmaceutical ancillary substances.



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